

1932

# ARCHIVES OF DISEASE IN CHILDHOOD.

EDITED BY

HUGH THURSFIELD, D.M., F.R.C.P. and REGINALD MILLER, M.D., F.R.C.P.

WITH THE HELP OF

H. C. CAMERON, M.D., F.R.C.P.

C. MAX PAGE, D.S.O., M.B., F.R.C.S.

H. A. T. FAIRBANK, D.S.O., M.B., F.R.C.S.

LEONARD G. PARSONS, M.D., F.R.C.P.

LEONARD FINDLAY, D.Sc., M.D.

G. F. STILL, M.D., F.R.C.P.

A. DINGWALL FORDYCE, M.B., F.R.C.P.(Edin.)

EDITOR OF THE *British Medical Journal*.

Vol. 6.

DECEMBER, 1931.

No. 36.

## CONTENTS

PAGE

- The Clinical Interpretation of Some Hæmorrhagic States. By W. G. Wyllie, M.D., M.R.C.P., and R. W. B. Ellis, M.A., M.D. .... 313
- A Case of Severe Anæmia in a New-born Infant. By Eric Pritchard, M.D., F.R.C.P., and Jean Smith, M.D., M.R.C.P. .... 325
- A Study of the Blood Cholesterol in Childhood. By Kathleen M. Ward, M.D., L.R.C.P., M.R.C.S. .... 329
- Gangrene in an Infant Associated with Temporary Diabetes. By R. D. Lawrence, M.A., M.D., M.R.C.P., and R. A. McCance, M.A., M.D., M.R.C.P., Ph.D. .... 343
- The Multiple Puncture Cutaneous Tuberculin Test. By W. S. Craig, B.Sc., M.B., Ch.B. .... 357
- Studies in Juvenile Rheumatism. By Christopher J. McSweeney, M.D., D.P.H. .... 367

*Index for Volume VI included.*

ISSUED BY THE BRITISH MEDICAL ASSOCIATION.

London: British Medical Association House

Tavistock Square, W.C. 1.

Yearly Subscription (6 numbers) 25/-

Single Number, 4/6

## GENERAL ADVISORY BOARD.

H. T. ASHBY (Manchester).  
A. D. BLACKADER (Montreal).  
W. R. BRISTOW (London).  
ALAN BROWN (Toronto).  
E. CAUTLEY (London).  
CAREY COOMBS (Bristol).  
GLEN DAVISON (Newcastle-on-Tyne).  
T. Y. FINLAY (Edinburgh).  
G. B. FLEMING (Glasgow).  
Prof. JOHN FRASER (Edinburgh).  
Prof. W. E. GALLIE (Toronto).  
Sir ARCHIBALD GARROD, K.C.M.G. (Oxford).  
J. F. GASKELL (Cambridge).  
G. R. GIRDLESTONE (Oxford).  
H. TYRRELL GRAY (London).  
ROBERT HUTCHISON (London).  
R. C. JEWESBURY (London).  
F. S. LANGMEAD (London).

C. P. LAPAGE (Manchester).  
W. L. MACCORMAC (Balham).  
HELEN MAYO (N. Adelaide).  
T. P. McMURRAY (Liverpool).  
CHARLES McNEIL (Edinburgh).  
A. E. NAISH (Sheffield).  
D. H. PATTERSON (London).  
W. J. PEARSON (London).  
F. J. POYNTON (London).  
T. G. PUGH (Cardiff).  
F. C. PYBUS (Newcastle-on-Tyne).  
Sir HUMPHRY ROLLESTON, Bt. (Cambridge).  
J. D. ROLLESTON (London).  
J. C. SPENCE (Newcastle-on-Tyne).  
E. H. M. STEPHENS (Sydney).  
G. BRUTON SWEET (Auckland, N.Z.).  
C. W. VINING (Leeds).  
E. H. WILLIAMS (Dunedin).

---

## NOTICE TO SUBSCRIBERS.

Subscriptions are payable to the Financial Manager of the British Medical Association who has charge of all financial matters concerning the ARCHIVES OF DISEASE IN CHILDHOOD. Address: British Medical Association House, Tavistock Square, London, W.C. 1.

## NOTICE TO CONTRIBUTORS.

All papers submitted for publication should be sent to Dr. Reginald Miller, 110, Harley Street, W. 1. All other editorial matters should be referred to Dr. Hugh Thursfield, 84, Wimpole Street, W. 1.

Papers sent for publication should be typewritten. Illustrations will usually be inserted in the text itself, and care should be taken that the text is marked to show the desired position of each illustration.

Charts and curves accompanying papers should be carefully drawn, on tracing linen. Any lettering on these drawings should be lightly inserted in pencil.

Contributors will receive one proof in page, but it is assumed that all but verbal corrections have been made in the original manuscript; an allowance at the rate of ten shillings per sheet of sixteen pages is made for alterations in the proof (printer's errors excepted), and contributors will be responsible for any excess.

Contributors will be supplied with reprints of their articles at cost price if application is made when returning proofs. An estimate of costs will be given if desired on application to the Financial Manager of the British Medical Association.

Papers which have been published become the property of the ARCHIVES and permission to republish must be obtained from the Editors.

# THE CLINICAL INTERPRETATION OF SOME HÆMORRHAGIC STATES

BY

W. G. WYLLIE, M.D., M.R.C.P., and R. W. B. ELLIS, M.A., M.D.\*

(From the Children's Department, Westminster Hospital, London.)

**Introduction.**—The differential features described in any text-book of medicine between purpura hæmorrhagica and hæmophilia would appear to make their confusion unlikely. In actual practice, however, it is often less easy to make a clear distinction. Between purpura hæmorrhagica and hereditary hæmophilia comes a varied group of cases, including sporadic and pseudo-hæmophilia and instances of hereditary and familial purpura hæmorrhagica. Moreover, a case that at one time may have the clinical appearance of hæmophilia, may at another time present the features of purpura. It is insufficiently recognized that petechiæ in the integument are not an essential symptom of purpura hæmorrhagica, and that spontaneous bleeding from the nose, gums, and kidneys, may occur in either of the conditions mentioned.

Primary purpuras have been classified as purpura simplex, purpura hæmorrhagica, purpura arthritica (Schönlein's disease), and Henoch's purpura. This subdivision has its clinical convenience, but there is no real justification for regarding these types as distinct diseases. Some authorities have attempted to isolate purpura hæmorrhagica from the others, on account of the thrombocytopenia by which it is usually characterized. A platelet deficiency, however, is not a constant finding in all cases of purpura hæmorrhagica, and has been observed occasionally in some of the other forms of primary purpura. Litten<sup>1</sup> regarded the primary purpuras as varieties of the same disease, influenced in different cases by individual circumstances. Tidy<sup>2</sup> and Thursfield<sup>3</sup> consider that no essential difference exists between the various types of primary purpura.

There are also certain cases of purpura hæmorrhagica which on blood examination are indistinguishable from the primary or idiopathic type, but which are definitely secondary to septic processes such as osteomyelitis and otitis media. In them a platelet deficiency is a common finding.

The object, then, of the present paper is to consider a number of cases characterized by a hæmorrhagic diathesis, and to attempt a somewhat more general survey of their relationship than is usually adopted. It will be useful as a preliminary to enumerate the usual text-book criteria of (essential) thrombocytopenic purpura and hæmophilia. This can conveniently be done in the form of a table (Table 1).

---

\* Under the tenure of a Wander Research Scholarship.

It is apparent that none of the clinical tests enumerated can be taken by itself as a positive proof of either condition, but collectively they facilitate the differentiation of hæmophilia from purpura hæmorrhagica.

A platelet reduction is also met with in other blood diseases, such as pernicious anæmia, aplastic anæmia and lymphatic leukæmia. The number of platelets, however, in some cases of purpura hæmorrhagica may be normal. In hæmophilia the number is usually, though not invariably, normal or raised.

The production of petechiæ by the method of passive congestion with a tourniquet can be obtained in endocarditis lenta, and we have had a positive result with this test in a case of hæmorrhagic nephritis.

A prolonged bleeding time, thrombocytopenia, and petechiæ may be observed in lymphatic leukæmia, and petechiæ may occur in such widely different conditions as meningitis of various forms, encephalitis, typhus, and in almost any form of septicæmia.

TABLE 1.

TEXT-BOOK DIFFERENCES BETWEEN ESSENTIAL THROMBOCYTOPENIC PURPURA AND HÆMOPHILIA.

	E. T. Purpura	Hæmophilia
Hereditary tendency.	Rare.	Present.
Sex.	Male and female.	Male, transmitted by female.
Hæmorrhage.	Frequently spontaneous.	Following direct injury.
Petechiæ.	Usually present.	Absent.
Tourniquet test.	Positive.	Negative.
Platelets.	Reduced.	Normal.
Bleeding time.	Prolonged.	Normal.
Clotting time.	Normal.	Prolonged.
Clot.	Retraction defective.	Fragile.
Spleen.	Frequently enlarged.	Not enlarged.

Spontaneous hæmorrhage from nose, kidneys, or gums, may occur in either of the conditions under discussion, and in hæmophilia ecchymotic extravasations from blunt trauma are not uncommon. The tests of greatest value in arriving at a diagnosis are the bleeding and clotting times of the blood.

In hæmophilia a diagnosis is easy, provided a hereditary tendency is ascertainable with occurrence in the male only. It is in the sporadic cases where doubt arises. Where a history of bleeding is not obtainable in two or three preceding generations the hereditary influence cannot be excluded, for the chromosomal defect responsible for the disease can be transmitted through the females of several generations without the occurrence of bleeders among the male progeny. It is, however, certain that true sporadic hæmophilia can occur, although some examples of so-called sporadic hæmophilia, in which full pathological investigations have not been carried out, are probably cases of purpura hæmorrhagica of a type in which petechiæ are absent.

The most characteristic features of purpura hæmorrhagica are held to be the spontaneous occurrence, or artificial production by tourniquet, of petechial

hæmorrhages; the liability to ecchymotic extravasations on minor injury; spontaneous bleeding from mucous membranes, nose, gums, bowel and sometimes kidney; and the prolonged bleeding time with normal clotting time in vitro. Splenic enlargement is a feature of many cases. In most instances the thrombocytes are reduced, but not necessarily in all. The critical level below which some form of bleeding is almost certain to be present is placed at 30,000 per c.mm. (the normal being 200,000 to 500,000), though exceptions have been recorded with a very low platelet count without the occurrence of bleeding.

Two types of purpura hæmorrhagica have been described. The acute, relapsing or intermittent, and the continuous. As stated by Frank, in the first type the state of the blood in the interval between attacks may be found to be normal. The diathesis renews itself at each subsequent attack, while in the continuous type an abnormal state of the blood is constant; though clinical manifestations of the disease are not always in evidence. After considerable bleeding the blood picture frequently shows a high relative lymphocytosis, which is one of the reasons why the disease may be confused with lymphatic leukæmia. A polymorphonuclear preponderance in purpura is taken as a favourable index of marrow activity. The disease has no sex partiality, and a greater number of cases occur in the pre-pubertal period than at other ages.

Instances of hereditary and familial purpura hæmorrhagica have been recorded. Recently McKay<sup>4</sup> has referred to three cases of hereditary purpura hæmorrhagica in which the platelet count was normal or raised, and Witts and Conybeare<sup>5</sup> have described the condition in two brothers, in both of whom the platelets were greatly reduced, while a sister died from epistaxis. Little and Ayres<sup>6</sup> reported a family in which the mother and six out of nine children were bleeders. Two female children showed a greatly prolonged bleeding time with a normal clotting time, and normal or very slightly diminished platelets.

Generally speaking it may be said that blunt trauma and lesions which are sufficient to produce bleeding in the purpuric patient are ineffectual in the hæmophilic. Venepuncture and subcutaneous injections are unattended by blood extravasation in the hæmophilic, but in cases of purpura bleeding commonly occurs at the site of needling.

As an important point of distinction between hæmophilia and purpura hæmorrhagica, Frank upholds the fact that following trauma, such as needling the lobe of the ear, there is in hæmophilia a short primary bleeding time, although after an interval there may be a prolonged after-bleeding. In purpura hæmorrhagica the primary bleeding is prolonged, but on ceasing is not repeated. Other writers have emphasized the fact that in purpura the clot-retraction in vitro may be defective, while in hæmophilia the clot retracts normally, but is abnormally fragile.

**Methods of investigation.**—The following methods of pathological investigation were employed in the cases reported below :—

BLEEDING TIME was calculated by Duke's<sup>7</sup> method, using his technique, the normal being placed at 2 to 3½ minutes. Although this investigation is undoubtedly of value, it should be remembered that its employment is entirely empirical. No really satisfactory explanation has been offered as to why it is normal in the great majority of cases of hæmophilia. A prolonged bleeding time is possibly associated in some way with defective clot-retraction.

CLOTTING TIME (except where otherwise stated) was estimated on capillary blood by the capillary tube method. Two lengths of standard capillary tube were filled with blood obtained by needle prick from the lobe of the ear, and were kept at 37° C. After two minutes the first tube was broken at intervals of 30 seconds until a continuous thread of clot was obtained between the two broken fragments. The second tube was then broken in the same way until clotting occurred, which was usually 15 to 30 seconds later than in the first tube owing to the less frequent manipulation of the second. The total time from the filling of the second tube to the occurrence of clot formation in it was taken as the clotting time (normal 2 to 4 minutes).

PLATELETS were counted per 1,000 red blood corpuscles in the Thoma Zeiss counting chamber, the blood being obtained from the finger by a needle prick made through a drop of 2 per cent. citrate solution. The drop of blood and citrate solution was transferred to a wax chamber by means of a freshly waxed pipette and further diluted with citrate solution. The counting chamber was filled with the fluid and allowed to stand for half an hour to allow the platelets to settle. The platelets per 1,000 R.B.C. were then counted. A red blood cell count was carried out in the usual way, and the platelets per c.mm. calculated. The majority of platelet counts were carried out in duplicate and the average value taken. Counts between 200,000 and 500,000 per c.mm. were considered as within normal limits.

SERUM CALCIUM was estimated by the method of Kramer and Tisdall<sup>8</sup>.

### Clinical reports and commentaries.

The following ten cases of abnormal bleeding in children illustrate certain inter-relationships both in their symptoms and in their pathological findings. By the criteria already described, the first four would be generally recognized as hæmophilia; Case 6 as Henoch's purpura; and Cases 7 and 8 as thrombocytopenic purpura. Case 5 has certain features in common with both hæmophilia and purpura, which render its classification problematical, while in the last two cases the diagnoses made were lymphatic leukæmia with osteomyelitis and Banti's disease respectively. Attention is particularly drawn to those features which may exist in common between the hæmorrhagic states, and render hard-and-fast distinctions difficult.

**Case 1.**—F.M., male, aged 5 years. One sibling, female, aged one year and three months, healthy. No family history of hæmophilia in the three preceding generations. Patient was first admitted to hospital November 16th, 1928, aged 2 years and 8 months, suffering from impetigo and carious teeth. The extraction of 8 teeth was followed by prolonged hæmorrhage, gradually ceasing after 9 days. A blood transfusion was given on the fourth day of bleeding.

On re-admission, 3.1.30, a right lower molar with pus at its root was extracted and the socket plugged. Hæmorrhage occurred intermittently, becoming more severe on the fourteenth day, and requiring blood transfusion.

Re-admission 20.2.31, with six days' bleeding from a bitten tongue. The bleeding ceased after three days.

**PATHOLOGICAL FINDINGS.** 12.12.28. Clotting time, 6 minutes; platelets, 300,000 per c.mm.

4.11.29. Clotting time, 6 minutes; platelets, 100,000 per c.mm.; R.B.C., 5,400,000; Hb., 66 per cent.; C.I., 0.55; W.B.C., 10,000; Polym. neutrophils, 45 per cent.; eosinophils, 4 per cent.; mononuclears, 6 per cent.; lymphocytes, 45 per cent.

8.1.30. Clotting time, 10 minutes.

20.1.30 (after considerable hæmorrhage). R.B.C., 2,800,000; Hb., 47 per cent.; C.I., 0.72; platelets, 560,000 per c.mm.

24.2.31. Bleeding time, 6 minutes; clotting time, 7 minutes; R.B.C., 3,600,000; Hb., 47 per cent.; C.I., 0.65; W.B.C., 7,800.

26.2.31. Platelets, 325,800 per c.mm.

16.3.31. Bleeding time,  $4\frac{1}{2}$  minutes; clotting time, 4 minutes.

**Case 2.**—J.J., male, aged  $4\frac{1}{2}$  years. There is one other child, a boy, aged 2 years, who has shown no tendency to bleed, and there is no history of bleeders in the mother's family, traced back through five generations.

The patient had oozing of blood from the navel 17 days after birth, which continued for 10 days. Since then he has had many hæmorrhages, epistaxis, prolonged bleeding after biting his lip, and from a pinprick of the lobe of the ear, and a hæmorrhage into the left knee joint. He also bruises very easily from blunt trauma, but has never shown spontaneous petechiæ, nor splenic enlargement.

**PATHOLOGICAL FINDINGS.** 4.12.30 (no hæmorrhage at this date). R.B.C., 3,768,000; W.B.C., 10,800; Polymorphonuclears, 33 per cent.; lymphocytes, 67 per cent.; platelets, 120,570 per c.mm.

19.2.31. Bleeding time, 4 minutes 15 seconds; clotting time, 10 minutes 30 seconds.

**COMMENT.**—Both the above cases show the clinical picture of hæmophilia, but in neither is there any traceable family history of abnormal bleeding. Case 2 especially, where the family history on the mother's side was traced back for five generations, indicates 'sporadic' bleeding. In both the clotting time is definitely, though not greatly, prolonged and the bleeding time slightly so. Diminished platelets were found in each case on one occasion, though in the first, where repeated estimations were carried out, subsequent platelet values were normal. The variation in clotting time seen in Case 1 is a not infrequent finding in hæmophilia.

**Case 3.**—W.B., male, aged  $6\frac{1}{4}$  years. The patient's mother was one of eight children (5 boys, 3 girls); her two eldest brothers were bleeders. The patient has two younger brothers, both bleeders. The history of the younger is given in detail below. The middle brother required blood transfusion recently for prolonged bleeding following extraction of teeth. Two older brothers and one sister have shown no abnormal bleeding.

Patient has had repeated blood transfusions for hæmorrhages following slight trauma since one year of age. Hæmaturia of short duration occurred September, 1930, and a large hæmatoma of the left leg followed the bite of an insect in the ensuing month. He was admitted to hospital on May 18th, 1931, with the left elbow swollen and discoloured, but with no history of trauma. Recovery was uneventful.

**PATHOLOGICAL FINDINGS.** 18.5.31. Clotting time, 9 minutes 12 seconds; bleeding time, over 10 minutes; clot retraction normal. R.B.C., 3,440,000; platelets, 509,120 per c.mm.; serum calcium, 9.4 mgrm. per cent.

**Case 4.**—A.B., brother of Case 3, aged 3 years 4 months. Patient bled from the navel for three days at birth. Since then he has had repeated oozings of blood following minor injuries, but has not required transfusion. He has twice been admitted to hospital, once for persistent bleeding lasting ten days from an abrasion of the lower lip, and once for extensive hæmatoma of scrotum and of lower abdomen following trauma.

**PATHOLOGICAL FINDINGS.** 30.12.30. R.B.C., 3,030,000; Hb., 44 per cent.; C.I., 0.7; W.B.C., 7,000; Polymorphonuclears, 59 per cent.; lymphocytes, 41 per cent.; platelets, 380,000 per c.mm. Bleeding time,  $3\frac{1}{2}$  minutes; clotting time, 9 minutes; serum calcium, 8.5 mgrm. per cent.

31.12.30. Prothrombin time (venous blood, Howell's method<sup>9</sup>), 76 minutes (approximately 5 times normal control).

**COMMENT.**—In contrast to the first two cases, Cases 3 and 4 adhere much more closely to the classical picture of hæmophilia. Not only are the family and clinical histories typical, but the blood findings include normal

platelets and definitely prolonged clotting time in both cases. Thus, while there is no question as to the diagnosis of hæmophilia, it is of considerable interest that the bleeding time in Case 3 is over 10 minutes, a finding completely at variance with the normal bleeding time usually described.

**Case 5.**—J.T., male, aged 10 years, with no family history of hæmophilia or purpura. The patient has bled freely from trivial injuries since infancy. At eight years of age a large swelling appeared on the right thigh, following trauma, and since then he has had several swellings of the shoulder and knee joints. In January, 1931, there was swelling of the right knee, extensive bruising of the upper chest, oozing from the gums, and a blood-stained discharge from the ears.

On admission to the Westminster Hospital the right knee showed fixed flexion at  $90^\circ$ , and the presence of a considerable effusion which was fluctuant in its upper and outer margins and pitted on pressure. There was no redness or tenderness. Glands were palpable in the neck and groins, and the spleen was enlarged one finger's breadth below the costal margin. The tonsils were enlarged and a bilateral aural discharge was present. The patient had a low grade temperature for three to four weeks in hospital, but subsequently became apyrexial. Spontaneous bleedings from the gums occurred repeatedly; on one occasion sufficiently severe to necessitate transfusion. There was also prolonged bleeding from a small head injury. The spleen remained slightly enlarged, but no further glandular enlargement occurred. The patient was discharged to convalescence after four months.

**PATHOLOGICAL FINDINGS.** On admission: Bleeding time, 13 minutes; clotting time, 45 minutes.

30.4.31. Bleeding time,  $6\frac{1}{2}$  minutes; clotting time, 21 minutes (venous). Blood calcium, 11.5 mgrm. per cent.

15.5.31. R.B.C., 4,230,000; Hb., 71 per cent.; C.I., 0.84; Polym. neutrophils, 72 per cent.; mononuclears, 2 per cent.; lymphocytes, 26 per cent.; platelets, 60,000.

21.5.31. Bleeding time,  $5\frac{1}{2}$  minutes; clotting time (capillary),  $6\frac{1}{2}$  minutes.

18.6.31 (after prolonged hæmorrhage from gums). R.B.C., 2,180,000; Hb., 35 per cent.; C.I., 0.83. Patient was transfused; blood Group II.

29.6.31. R.B.C., 2,500,000; Hb., 43 per cent.; C.I., 0.86.

**COMMENT.**—It has already been emphasized that certain cases exist which show features in common with both hæmophilia and purpura, and provide as it were a half-way house between the two conditions. The above case is a good example. He was admitted to hospital with what was regarded as a hæmophilic joint, and in view of the very greatly prolonged clotting time (45 minutes) and the negative tourniquet test, he was shown at the Children's Section of the Royal Society of Medicine (April, 1931,) with that tentative diagnosis. In favour of purpura, however, were the considerably prolonged bleeding time, the reduction of platelets and the enlarged spleen. The clotting time was subsequently reduced to  $6\frac{1}{2}$  minutes and repeated spontaneous hæmorrhages from the gums became the chief clinical feature of the case. It is probable that if he had been seen for the first time at this stage a diagnosis of purpura would have been made. The picture was somewhat complicated by the presence of a septic focus and a low grade temperature on admission, and it is possible that the reduction of platelets may have been associated with this. No petechial lesions, however, occurred at any time and the tourniquet test was consistently negative.

**Case 6.**—D.R., male, aged 5 years and 4 months, was admitted to hospital on July 15th, 1930, with a history of sore throat and vomiting for 3 days, occurring 3 weeks before admission. The day before admission the child complained of severe pains in the right knee, followed by pains in the left leg and both arms. The temperature was  $101^\circ$ . On examination he appeared well-

nourished and of good colour. Fine purpuric spots were scattered over the buttocks and perineum and in a patch behind the right knee. The right knee and shoulder were painful on passive movement. Two days later the abdomen became distended and diffusely tender, especially in the left hypochondrium. The spleen was not palpable. There were also swelling and tenderness over the lumbar spines. Radiographs of the right knee and lumbar spines were negative. In the course of the following two days the abdominal pain increased and there was evidence of free peritoneal fluid. Haemorrhage from the bowel occurred on three consecutive days. The general condition then rapidly improved and the child was discharged home with no physical signs of disease. When seen nine months later he had had no recurrence of purpura, or of haemorrhage from the bowel. No history suggestive of allergy was obtained.

**PATHOLOGICAL FINDINGS.** 16.7.30. R.B.C., 5,840,000; Hb., 77 per cent.; C.I., 0.60; W.B.C., 10,200; Polym.neutrophils, 76 per cent.; eosinophils, 3 per cent.; mononuclears, 1 per cent.; lymphocytes, 20 per cent.; platelets, 650,000.

20.4.31. R.B.C., 4,400,000; Hb., 81 per cent.; C.I., 0.92; W.B.C., 6,200; Polym.-neutrophils, 42 per cent.; eosinophils, 3 per cent.; mononuclears, 1 per cent.; lymphocytes, 52 per cent.; transitionals, 2 per cent.; platelets, 600,000. Bleeding time, 1 minute 50 seconds; clotting time, 3 minutes.

**COMMENT.**—This case shows the characteristic picture of Henoch's purpura, a condition which has been considered by many writers to be due to an allergic diathesis. It will be noted that the occurrence of spontaneous bleeding from the bowel and of purpuric skin lesions was here unassociated with any reduction in platelets, whose number was, in fact, abnormally high. As may occur in all varieties of purpura the onset was accompanied by severe arthritic pains and was preceded by an upper respiratory infection.

**Case 7.**—I.M., female, aged 6 years. Patient was admitted with a history of repeated and severe epistaxis for two weeks. There was no previous history of bleeding and her general health had been good. A brother, aged 7 years, was healthy. On admission the patient showed scattered purpuric lesions on the back, abdomen and legs, with oozing of blood from nose and gums, and extensive ecchymoses on the limbs. The heart was dilated and a systolic murmur was heard at the base. There was no evidence of local sepsis. The occurrence of repeated epistaxis necessitated blood transfusion (300 c.cm.) nine days after admission, and again two days later. The spleen was removed by Mr. Tudor Edwards after the second transfusion. The organ weighed 60 gm. and showed some perisplenitis. The patient was transfused on the evening of the day of operation and again ten days later. The operation did not appear to have any immediate effect on the bleeding, and a fifth transfusion was given before her discharge from hospital. She was re-admitted six weeks later for recurrent epistaxis since discharge and was given intramuscular injections of normal horse serum in an attempt to produce a protein shock. The last injection was followed in 24 hours by transient joint pains and a very extensive fine purpuric rash. When seen in May, 1931, eight months after splenectomy, the patient still showed an extensive purpuric eruption and ecchymoses on the limbs, with a recent history of two severe attacks of epistaxis.

**PATHOLOGICAL FINDINGS.** On admission: R.B.C., 2,143,000; Hb., 45 per cent.; C.I., 1.00; W.B.C., 7,200; Polym.neutrophils, 62 per cent.; mononuclears, 6 per cent.; lymphocytes, 32 per cent.; platelets, 125,000 per c.mm. The patient bled profusely when pricked for blood count. The platelet count fell to 6,000 a month after splenectomy, with a subsequent rise to 45,000 two months later. Clotting time was normal throughout.

Bleeding time:—

1 month after operation,	18	minutes.
6 weeks     "     "	7½	"
3 months   "     "	23	"
8 months   "     "	18	"

May, 1931 (8 months after splenectomy). R.B.C., 4,110,000; W.B.C., 13,000; Polym.neutrophils, 51 per cent.; eosinophils, 1 per cent.; transitionals, 1 per cent.; mononuclears, 2 per cent.; lymphocytes, 45 per cent.; platelets, 12,000.

Report by Dr. Braxton Hicks on spleen: There is a general increase in connective tissue, and the splenic pulp appears as an open sponge, particularly at the periphery. The lymphocytes have for the most part disappeared, with the exception of the Malpighian corpuscles.

COMMENT.—The case shows the features of a typical thrombocytopenic purpura, prolonged bleeding time, reduced platelets, normal clotting time, and clinically the occurrence of spontaneous purpuric lesions and free hæmorrhages. There was no family history of bleeding nor evidence that the condition was of secondary origin. Neither the clinical nor pathological condition was appreciably benefited by splenectomy, and the marked rise in platelets which frequently follows this operation did not occur.

Case 8.—V.L., female, aged 7 years, 4 months. There was no family history of abnormal bleeding. Since the age of 3 years the patient has suffered from epistaxis, excessive bruising, and purpuric lesions. A severe hæmorrhage followed the extraction of three teeth in June, 1929, on account of which she was admitted to hospital for one week. At this time it was noted that the tonsils and tonsillar glands were both enlarged, and that purpuric lesions were present. Occasional epistaxis occurred during the succeeding fifteen months.

In November, 1930, the left ear began to discharge and blood appeared in the urine, both hæmaturia and aural discharge continuing until after tonsillectomy was performed in January, 1931. Blood transfusions were given before and after operation, which was accompanied by considerable hæmorrhage. Pus from a submental abscess, which developed one week later, grew streptococci in pure culture. The urine cleared in March, 1931. A cortical mastoid operation was next performed on March 16th by Mr. Chubb. The mastoid cortex and cells were found filled with pus and polypoid granulation tissue: the dura was exposed and showed early involvement. The following day the urine again contained blood in large amount, the hæmaturia persisting for several weeks.

#### PATHOLOGICAL FINDINGS.

22. 7.29.	Platelets, 203,000.	R.B.C., 4,600,000; Hb., 81 per cent.
24. 9.29.	„ 100,000.	
7.11.30.	„ 49,000.	Bleeding time, 6 minutes; clotting time, 5½ minutes.
6. 1.31.	„ 56,000.	„ „ 10½ „ „ „ 4 „
11. 2.31.	„ 30,000.	R.B.C., 3,570,000; Hb., 58 per cent..
16. 2.31.	„ none seen.	„ 2,710,000; „ 49 „
9. 3.31.	„ 5,000.	„ 4,500,000; „ 71 „
14. 3.31.	„ 2,000.	„ 4,020,000; „ 68 „

COMMENT.—The above case illustrates the close association which may exist between purpura hæmorrhagica and sepsis. While we cannot here definitely attribute the earliest symptoms to an infective cause, it was, however, noted that septic tonsils were present when the child first came under observation, and the simultaneous occurrence of aural discharge and hæmaturia in November, 1930, was striking. Similarly, after the hæmaturia had ceased, an exacerbation of the renal bleeding immediately occurred when an infected mastoid was opened up.

It is possible that certain cases of co-called ' hæmorrhagic ' or glomerular nephritis, in which the close association with tonsillar or other infection is well recognized, should be considered as falling into the same group as purpuric hæmaturia. The production of petechiæ by the tourniquet in one such case has already been mentioned.

The role of hæmolytic streptococci in the causation of purpura has recently been discussed by Langmead<sup>10</sup>. In this case a streptococcus was obtained from pus from a submental abscess.

**Case 9.**—J.S., female, aged 4 years, no relevant family history. The previous health was good with the exception of swollen cervical glands one year before admission.

Patient was admitted to hospital on July 30th, 1929, with several weeks' history of pallor and loss of appetite. For 5 days she had been drowsy and suffered from severe diarrhœa which had become bloody. For two days petechial lesions had appeared on the buttocks and limbs, and extensive bruising had occurred on both legs. On examination, the patient showed marked pallor of the mucous membranes, with bilateral enlargement of the cervical glands, and a few shotty glands were in the axillæ and groins. The throat appeared healthy, the liver was enlarged two fingers' breadths below the costal margin, but the spleen was not palpable. A soft systolic murmur was heard at the apex of the heart. Scattered petechiæ were present on the abdomen, buttocks and limbs, and extensive ecchymoses on both legs. The temperature was 102°.

In view of the severe degree of anæmia the patient was given a blood transfusion on August 3rd, which was followed by some improvement in her general condition. Six days later she developed a fluctuant swelling over her right tibia, which when opened and evacuated appeared to be an infected hæmatoma. She continued to run an irregular temperature. Radiographs (17.8.29) showed periostitis of the right tibia with presence of a small sequestrum. Subsequently recurrent crops of petechial lesions occurred on the buttocks, and two abscesses in the buttocks required to be opened and drained. *Staphylococcus aureus* was obtained on culture. On discharge there was some improvement in the general condition, but one month later severe anæmia and glandular enlargement were evident. The patient died some weeks later while at home, but a post-mortem examination was not obtained.

TABLE 2.  
PATHOLOGICAL FINDINGS IN CASE 9.

Date	R.B.C.	Hb.	C.I.	W.B.C.	Pmn. %	Eosin. %	Mon. %	Lymph. %	Platelets
31.7.29	2,300,000	28	0.7	2,300	14	0	11	75	—
19.8.29	4,230,000	64	0.76	9,400	57	0	0	43	100,000
28.8.29	—	81	—	—	59	1	8	32	—
16.9.29	4,000,000	70	0.87	8,800	30	4	6	60	—
26.9.29	4,420,000	78	0.88	7,800	3	1	1	95	—
19.8.29*									

\*Clotting time, 4½ minutes. Prolonged bleeding took place from needle wound made for blood counts. Agglutination against *B. typhosus*, *B. paratyphosus* A. and B., negative.

**COMMENT.**—From the blood count a provisional diagnosis of lymphatic leukæmia was made in this case. It will be seen that although considerable temporary improvement occurred in the blood picture following transfusion, the last differential count showed 95 per cent. of the white cells were of the lymphocytic series. The picture was complicated by the occurrence of osteomyelitis of the right tibia. Associated with these conditions, the patient showed the typical features of purpura hæmorrhagica, purpuric lesions of the skin, spontaneous bleeding from mucous membranes, thrombocytopenia, prolonged bleeding time and a normal clotting time.

**Case 10.**—R.B., female, aged 6 years. Six months before admission the patient had an attack of jaundice and malaise lasting for five weeks following infection of left maxillary antrum. Next, she had spontaneous bleeding from the gums, dark urine and black stools on several occasions, and recurrent crops of 'dark spots' (? telangiectases) on the skin which faded gradually with change of colour. The previous health had been good. There was no family history of either jaundice or abnormal bleeding.

On admission the patient showed extensive telangiectases on the face and a few similar lesions on the left forearm and right hand. Both liver and spleen were enlarged two fingers

breadths below the costal margin and were firm and non-tender. The patient was given a transfusion of whole blood and the spleen removed the following day. At operation the liver was found to be in a condition of early cirrhosis. On discharge from hospital the patient was free from symptoms.

**PATHOLOGICAL FINDINGS.** 16.4.30 (before operation). R.B.C., 4,120,000; Hb., 80 per cent.; C.I., 0.97; W.B.C., 7,200; Polym.neutrophils, 39 per cent.; mononuclears, 10 per cent.; lymphocytes, 51 per cent. Fragility: hæmolysis began in 0.5 per cent. saline (control 0.45 per cent.), and was complete in 0.4 per cent. saline (control 0.35 per cent.).

24.4.30 (before operation), platelets, 71,000 per c.mm.

5.5.30 (9 days after operation), R.B.C., 2,760,000; W.B.C., 43,800; Polym.neutrophils, 89 per cent.; mononuclears, 0; lymphocytes, 9 per cent.; basophils, 2 per cent.; platelets, 250,000 per c.mm.

21.5.30. R.B.C., 6,130,000; platelets, 210,000 per c.mm.

3.9.30. R.B.C., 4,800,000; Hb., 86 per cent.; C.I., 0.9; W.B.C., 6,500; Polym.neutrophils, 43 per cent.; eosinophils, 1 per cent.; lymphocytes, 52 per cent.; mononuclears, 2 per cent.

Report by Dr. Braxton Hicks on spleen (removed at hospital): Weight 7½ oz. The spleen exhibits the changes usually seen in splenomegaly with anaemia, only to a slighter degree. There is general increase in the fibrous tissue. Not only is the capsule thickened, but the trabeculae and Malpighian corpuscles and pulp show excess of fibrous tissue. The characteristic fibrous sponge tissue of the pulp, with disappearance of the pulp cells, is well seen particularly at the edge of the spleen.

**COMMENT.**—The above case is clearly one of Banti's disease in which both spleen and liver showed evidence of early fibrosis. It will be seen that the clinical history includes the presence of skin lesions, though of a different type from those seen in purpura. Spontaneous bleeding occurred from the gums, and the platelets were considerably reduced when first estimated but rose after splenectomy. Thus the case shows certain points of similarity to purpura hæmorrhagica, although the underlying ætiology is probably quite different. The occurrence of telangiectases suggests a possible relationship with a group of cases described by Parkes Weber<sup>11</sup>, in which familial or non-familial telangiectases of congenital-developmental nature were associated with a hæmorrhagic tendency.

#### Discussion.

In arriving at a satisfactory conception of the causes of abnormal bleeding, the three factors that may be involved must be considered. These are the platelets, the permeability of the capillary endothelium, and the blood plasma. Thus in the case of hæmorrhagic purpura where the process of bleeding involves a diapedesis of red blood cells through unbroken capillary walls, the blood platelets, which in the majority of cases are much reduced, and the capillary endothelium have been variously held responsible. In typical hæmophilia, on the other hand, where bleeding does not occur with intact capillaries and where the platelets are normal or slightly raised in number, the blood plasma is generally regarded as being the defective element.

The number of classifications of purpura advanced is in itself an index of how little is known of its essential causation. Denys<sup>12</sup> and later Frank<sup>13</sup> both considered that reduction in the number of platelets should be regarded as the factor responsible for hæmorrhage. Tidy<sup>2</sup> on the other hand insists that no clinical grouping corresponds with the reduction of platelets, and that several of Frank's original 'thrombopenic' cases would have to be classified

clinically as purpura simplex, i.e., showing petechial hæmorrhages but no free bleeding, whilst free bleeding may occur in purpura without the platelets being diminished. Tidy regards the reduction of platelets in the general circulation as secondary to their becoming adherent to damaged capillary walls in an attempt to prevent diapedesis. The experimental work of Bedson<sup>14</sup> is of interest in this connection since it suggests that neither reduction of platelets nor damage to capillary endothelium can alone produce purpura in rabbits, but when both factors are combined purpuric lesions result. Similarly with regard to the role of the spleen considerable divergence of opinion exists, Kaznelson<sup>15</sup> and others holding that destruction of platelets occurs in this organ, while Frank<sup>16</sup> supports the view that the thrombocytopenia is due essentially to diminished production by the bone marrow, which would suggest that the spleen excretes a myelotoxin. It is certain, however, that in many cases splenectomy results in a rapid rise in platelets, though these may subsequently fall again to normal or subnormal levels.

It is clear that sepsis may be intimately connected with the production of hæmorrhagic purpura, this being well illustrated by Case 8 and by two cases recently published by Coke<sup>17</sup>. In all of these the platelets were greatly reduced. The interpretation put on these findings will depend on the view of platelet action adopted. Sepsis may either act in these cases by direct suppression of platelet formation by the bone marrow, or may have a damaging effect on the capillary endothelium. The case of hæmorrhagic nephritis already referred to in which the tourniquet test produced an extensive crop of purpuric lesions, but in which the platelets were not reduced, suggests that the latter may be the case.

Neither the platelets nor the capillary endothelium appear to be defective in hæmophilia, and the fact that unwashed platelets in this condition were found more resistant to lysis than those of normal blood is probably explained by their being surrounded by a film of relatively stable plasma (Pickering<sup>18</sup>). It is this abnormal stability of the plasma that is the characteristic feature of the disease. All the known elements of the plasma appear to be normally present, and though rare cases of greatly delayed clotting *in vitro* due to lack of fibrin (Opitz and Magda<sup>19</sup>, Rabe and Salomon<sup>20</sup>) and deficient calcium (Hess<sup>21</sup>) have been described, they have little in common with true hæmophilia. Addis<sup>22</sup> concluded that the abnormal stability of hæmophilic plasma was due to a prolongation of the time of change of prothrombin into thrombin, and Pickering and Gladstone<sup>23</sup> suggest that this represents 'a persistence or re-appearance in adult life of an embryonic condition of the plasma.'

From the pathological standpoint it would appear, therefore, that in purpura we have a 'platelet-capillary' complex responsible for hæmorrhage, while in hæmophilia the plasma is abnormal. Both these factors may be inherited or both may arise *de novo*. The mode of transmission differs in the two cases, however, since the hæmophilic factor is sex-linked while the purpuric diathesis affects males and females equally. It is of interest to find, therefore, that purpura hæmorrhagica occurs not infrequently in the females of hæmophilic families (Hess<sup>24</sup>). Bauer and Wehefritz<sup>25</sup> have described thrombocytopenia in such cases.

Although it is difficult to explain satisfactorily on a pathological basis a relationship between hæmophilia and purpura, it should be clearly recognized that such exists. The evidence for their relationship is:—

1. The occurrence of abnormal bleeding of purpuric type in the females of some hæmophilic families with, in certain cases, the full picture of thrombocytopenic purpura.

2. The occurrence of isolated features characteristic of purpura in certain cases of hæmophilia, and vice versa.

3. Occasionally alternation of the hæmophilic and purpuric state may occur in the same individual. An excellent example of this is furnished by a case described by Pickering<sup>18</sup>, and our fifth case (J.T.) illustrates the same point to some extent.

Similarly, the same clinical and pathological picture may be present in primary purpura arising sporadically or familial in origin, and in purpura which is secondary to sepsis, toxins, or other pathological conditions. In both primary and secondary types the platelet-capillary complex is affected.

In considering cases of abnormal bleeding, therefore, it is well to remember that although the great majority can be conveniently classified, a number of atypical cases will remain to remind us that much of our classification is arbitrary and that no absolute division exists between certain disease entities.

We wish to express our sincere thanks to Dr. Donald Paterson and to Mr. Rock Carling for permission to report cases under their care, and to Dr. Braxton Hicks for his help and supervision of the pathological examinations.

#### REFERENCES.

1. Litten, M., *Speciele Pathol. u. Therap.* (Nothnagel), 1898, VIII, part 3, 343.
2. Tidy, H. L., *Lancet*, Lond., 1926, ii, 365.
3. Thursfield, J. H., *Diseases of Children*, Garrod, Batten, Thursfield, and Paterson. Lond., 1929, 477.
4. McKay, W., *Quart. J. Med.*, Oxf., 1931, XXIV, 285.
5. Witts, L. J. & Conybeare, E. T., *Proc. Roy. Soc. Med.*, Lond., 1931, XXIV, 709.
6. Little, W. D., & Ayres, W. W., *J. Am. Med. Ass.*, Chicago, 1928, XCI, 1251.
7. Duke, W. W., *Ibid.*, 1910, LV, 1185.
8. Kramer, B. & Tisdall, F. F., *J. Biol. Chem.*, Baltimore, 1921, XLVII, 475.
9. Howell, W. H., quoted by Todd, J. C., *Clinical Diagnosis by Laboratory Methods*, Lond., 1924, 249.
10. Langmead, F., *Arch. Dis. Childh.*, Lond., 1931, VI, 255.
11. Weber, F. P., *Brit. J. Child. Dis.*, Lond., 1924, XXI, 198.
12. Denys, J., *La Cellule*, Louvain, 1887, III, 445.
13. Frank, E., *Berlin klin. Woch.*, Berlin, 1915, LII, 454, 490, 961.
14. Bedson, P. H., *J. Path. and Bact.*, Edin., 1922, XXV, 94. *Ibid.*, 1924, XXVI, 176.
15. Kaznelson, P., *Zt. f. klin. Med.*, Berlin, 1919, LXXXVII, 133.
16. Frank, E., *Schittenhelm's Krankheiten des Blutes*, Berlin, 1925, II, 289.
17. Coke, H., *Brit. Med. J.*, Lond., 1931, i, 535.
18. Pickering, J. W., *The Blood Plasma*, Lond., 1928, 200 and 203.
19. Opitz, H. & Magda, F., *Jahr. f. Kinderheil.*, Berlin, 1921, XCIV, 374.
20. Rabe, F. & Salomon, E., *Deut. Arch. f. klin. Med.*, Leipzig, 1920, CXXXII, 240.
21. Hess, A. F., *Bull. Johns Hopkins Hosp.*, Baltimore, 1915, XXVI, 372.
22. Addis, T., *J. Path. and Bact.*, Edin., 1911, XV, 427.
23. Pickering, J. W. & Gladstone, R. J., *Lancet*, Lond., 1925, i, 602.
24. Hess, A. F., *Arch. Int. Med.*, Chicago, 1916, XVII, 203.
25. Bauer, K. H. & Wehefritz, E., *Archiv. f. Gynakol.*, Berlin, 1924, CXXI, 462. *Ibid.*, 1926, CXXIX, 1.

# A CASE OF SEVERE ANÆMIA IN A NEW-BORN INFANT

BY

ERIC PRITCHARD, M.D., F.R.C.P., and JEAN SMITH, M.D., M.R.C.P.

(From the Infants Hospital, Westminster, London.)

Slight degrees of anæmia in the new-born, with or without jaundice, are common enough, but cases of the degree of severity at all comparable to the one we are about to describe, are extremely rare. We have been able to discover in the literature records of investigations of only fifteen cases which deserve to be classified in this category, although fourteen other cases have been observed but not described (Grulee<sup>11</sup>, Foote<sup>8</sup>, McClelland<sup>13</sup>, Blackfan, Baty and Diamond<sup>2</sup>). All the cases in the literature are, we believe, included in the accompanying table, with the exception of four of massive hæmorrhage into the supra-renal capsules, published by D. P. Arnold<sup>1</sup>. These latter cases do not contain sufficient details with respect to the blood conditions to be included in the list.

The cause of the anæmia in most, if not in all, of these cases is uncertain. It may be concluded from their histories that they were all examples of secondary anæmia, for the reason that the symptoms came on a few days after birth—i.e., from the third to the seventh day, the common period of neonatal hæmorrhages,—and rapidly disappeared, either spontaneously or after simple treatment. Such results hardly could have occurred had they been due to defects in the hæmopoietic mechanisms. On the other hand, it is difficult to conceive how the site of an internal hæmorrhage sufficiently large to account for the symptoms could fail to be recognized.

In our own case we suspected a hæmorrhage into the left suprarenal gland for two reasons. First, a somewhat indefinite swelling could be felt in the position of this organ, but its presence could not be confirmed by X-ray examination, made when the infant was one month old. Secondly, the rather startling symptoms corresponded very closely with those recorded by Arnold<sup>1</sup> in new-born infants in four examples of massive hæmorrhage into the supra-renal capsules, two of which were confirmed by post-mortem examination. If our conclusions are correct, it is possible that similar hæmorrhages may have occurred in some of the other cases recorded without attracting attention. The striking similarity of the blood picture in these cases of anæmia in the new-born to that of an acute post-hæmorrhagic anæmia, has been noted by Pasachoff and Wilson<sup>14</sup>, although post-mortem examination in their case showed no gross hæmorrhage. Foote<sup>8</sup> has suggested that an occult hæmorrhage in combination with an insufficient reserve of iron may be of ætiological importance.

TABLE SHOWING 12 CASES OF SEVERE ANEMIA IN NEW-BORN INFANTS.

Author	Age	Red cells	Abnormal red cells	Hb. %	C.I.	White cells	Polymorpho-nuclears	Lympho-cytes	Platelets	Remarks—course of treatment
1. Pritchard and Smith	10th day	750,000	—	10	0.67	74,000	35	62	—	Normal fragility: Van den Bergh indirect +; 2 blood transfusions: 35 and 25 c.cm.
	13th "	1,900,000	Marked aniso- and poikilocytosis. Many more nucleated reds than in previous test.	20	0.53	42,000	30	64	—	Van den Bergh indirect +, but weaker.
	17th "	2,250,000		36	0.8	—	13	66	—	Indirect Van den Bergh = weak +
	23rd "	3,200,000	Immature forms much less frequent.	47	0.74	9,500	30	62	—	Van den Bergh —
	28th "	3,700,000	Few immature cells present.	58	0.78	8,700	32	66	—	Still rather pale: doing well. Weight 6 lb. 15 oz.
	35th "	4,200,000	Few immature cells present.	60	0.71	7,700	—	—	—	Cheeks pink. Weight 7 lb. 11 oz.
2. Ecklin <sup>6</sup>	12th day	2,500,000	Anisocytosis, poikilocytosis, basophilia, erythroblasts.	32	0.64	40,000	39.6	57.8	—	No special treatment. Blood picture normal by 7th month.
3. Donnelly <sup>5</sup>	20th day	918,000	—	20	1.0	29,200	5.5	42	—	Transfused with 100 c.cm. citrated blood into sinus.
	24th "	—	—	45	—	—	—	—	—	2nd transfusion 70 c.cm.
	28th "	—	—	35	—	—	—	—	—	Normal blood picture at 6 months.
4. Sanford <sup>15</sup>	1 hour	2,500,000	—	48	—	68,400	60	35	Normal	No special treatment.
	9th day	2,900,000	—	78	—	11,000	—	—	—	—
	30th "	3,720,000	—	80	—	—	—	—	—	—
5. Bonar <sup>3</sup>	13th day	1,200,000	Aniso- and poikilo-cytosis	31	1.3	18,000	54	43	—	No special treatment.
	3 weeks	1,450,000	—	23	—	6,000	—	—	—	—
	1 year	4,460,000	—	90	—	9,700	—	—	—	—

6. Sidbury <sup>6</sup>	14th day	800,000	—	10	—	28,000	46	—	—	Two transfusions—150 c.cm., blood then rose to an Hb. 44% and red cells 2,400,000. One week later 2nd transfusion 160 c.cm. Hb. 40%, red cells 2,600,000. Wonderful recovery.
7. Canino <sup>4</sup>	12th day	2,500,000	Erythroblasts megaloblasts, aniso- and poikilocytosis.	45	0.9	14,500	42	33	—	No treatment.
8. Ehrmann <sup>7</sup>	5th day 10th day	1,228,000 1,776,000	— Marked polychromasia.	28 35	1.2 —	20,550 20 300	36 —	56 —	— —	Slightly increased fragility of red cells. Haemolysis began at 0.6% completed at 0.44%. 60 c.cm. blood intraperitoneally on 7th day. 100 c.cm. on 12th day. Normal blood count at 7 months.
9. Happ <sup>12</sup>	14th day 16th " 4 weeks 8 " 12 " 17 " 30 "	1,088,000 1,592,000 3,771,000 3,376,000 3,672,000 4,808,000 4,672,000	Aniso- and poikilocytosis Moderate polychromasia No abnormal cells. — — — —	40 33 62 55 56 74 78	— — — — — — —	11,200 10,900 6,200 10,900 9,200 — 13,900	30 30 31 44.5 26 — 25	50 67 59 53.5 70 — 70	Normal " " " " " "	On 17th, 20th and 34th day, intraperitoneal blood transfusions given. Ferrum reductum given in milk. At 12 weeks liver and broth added to milk diet. Infant normal at 17 weeks.
10. Greenthal <sup>10</sup>	1st day 4th " 6th " 4 months	1,780,000 4,150,000 5,370,000 4,500,000	Moderate anisocytosis, few nucleated red cells. — — —	48 80 90 —	1.3 1.0 — —	17,000 9,400 — —	76 74 — —	18 25 — —	— 320,000 — —	3rd day 100 c.cm. whole blood (father's) given. — — —
11. Gelston and Sappington <sup>9</sup>	7 days	2,300,000	Slight aniso- and poikilocytosis polychromatophilia.	42	—	12,400	56	41	—	Three transfusions.
12. Pasachoff and Wilson <sup>14</sup>	5th day	390,000	Slight aniso- and poikilocytosis, occasional normoblasts.	8	1.0	16,800	24	53	242,000	Death before transfusions given.

**Clinical report.**

The following is a short account of our case :—

R.B., male, was born on June 10th, 1931. The mother, a rather delicate woman, had two other children, aged respectively four and one-and-a-half years. She had been examined during pregnancy at the ante-natal clinic at Queen Charlotte's Maternity Hospital, and she was attended at her own home by a midwife from this hospital under the supervision of the district Medical Officer, Dr. Florence Parsons. The infant, who at birth weighed 5½ lb., was noticed to be slightly jaundiced on the second day, but gave no cause for anxiety till the 7th day, when he was observed to be somewhat pale. The pallor increased rapidly during the 8th and 9th days, and it became so extreme by the 10th day that he was sent by Dr. Parsons to the Infants Hospital.

On admission, the infant was regarded as being in extremis, the pulse was 130 and extremely small. Respirations were 90, and of a gasping character. The temperature as recorded by a sub-normal thermometer, was below 90° F. The skin was absolutely colourless, and the mucous membrane of the lips a pale straw colour. The spleen was just palpable below the ribs, and the abdominal veins were slightly distended. Within a quarter of an hour of admission, the child's blood was grouped and 35 c.cm. of blood transfused into the longitudinal sinus. Owing to his collapsed condition, it was considered inadvisable to give the full amount for his age, namely, 10 c.cm. per pound weight, so only the above quantity of citrated blood was given at the first transfusion, but it was followed 5 hours later by another injection of 25 c.cm. The condition next morning had greatly improved, respirations had fallen to 50, and the temperature was normal. On the 14th day, the mother was admitted to hospital and from that time forward the child was breast-fed. Apart from these transfusions the only treatment given to the infant was the daily administration of small doses of extract of red-marrow, while iron and arsenic were given to the mother to raise the iron-content of her milk. The blood count which on admission showed only 750,000 red cells and a hæmoglobin percentage of 10, rapidly improved. Three days later the red cells were 1,900,000 in number and the hæmoglobin 20 per cent. Further details of progress are given in the table.

**Note.**—It is remarkable that in a case of such extreme anæmia, almost certainly due to internal hæmorrhage, there was not more definite evidence to point to the seat of the hæmorrhage. The rapidity of recovery was remarkable, and there can be little doubt that the infant would have died had not treatment by blood-transfusion been promptly carried out. Recovery was possibly accelerated by the presence of a depot of blood-clot due to an internal hæmorrhage, which served as material for hæmatopoiesis, and in this connection it is interesting to note that the X-ray film of the thorax showed enlargement of the costal epiphyses, suggestive of activity of the bone marrow in these situations.

**REFERENCES.**

1. Arnold, D. P., *Am. J. Dis. Child.*, Chicago, 1930, XL, 1053.
2. Blackfan, K. D., Baty, J. M., & Diamond, L. K., *Anæmias of Childhood*, N.Y., 1930, IX, 545.
3. Bonar, B. E., *Am. J. Dis. Child.*, Chicago, 1927, XXXIII, 226.
4. Canino, R., *La Pediatria*, Naples, 1927, XXIII, 1299.
5. Donnally, H. H., *Am. J. Dis. Child.*, Chicago, 1924, XXVII, 369.
6. Ecklin, T., *Monatschr. f. Kinderh.*, 1919, XV, 425.
7. Ehrmann, E. W., *Am. J. Dis. Child.*, Chicago, 1929, XXXVII, 138.
8. Foote, J. A., *Ibid.*, 1930, XXXIX, 1302.
9. Gelston, C. F. D., & Sappington, E. E., *Ibid.*, 1930, XXXIX, 807.
10. Greenthal, R. M., *Am. J. Med. Sci.*, Philad., 1930, CLXXIX, 66.
11. Grulee, C. G., *Nebraska Med. J.*, 1929, XIV, 97.
12. Happ, W. M., *Arch. Ped.*, N.Y., 1930, XLVII, 171.
13. McClelland, J. E., *Abstr. Am. J. Dis. Child.*, Chicago, 1928, XXXV, 732.
14. Pasachoff, H. D., & Wilson, L., *Ibid.*, 1931, XLII, 111.
15. Sanford, H. N., *Ibid.*, 1925, XXX, 19.
16. Sidbury, J. B., *J. Am. Med. Ass.*, Chicago, 1927, LXXXIX, 855.

# A STUDY OF THE BLOOD CHOLESTEROL IN CHILDHOOD\*

BY

KATHLEEN M. WARD, M.D., L.R.C.P., M.R.C.S.

(From the laboratory of the Royal Liverpool Children's Hospital.)

## I. THE BLOOD-CHOLESTEROL LEVEL IN HEALTHY CHILDREN.

**Previous investigations.**—From a perusal of the literature it appears that the subject of the blood-cholesterol level in healthy children has not been attacked systematically hitherto. Much work has been done on the normal percentage of cholesterol in both the whole blood and the plasma of adults, though many differing methods have been employed. More estimations have been made on the blood of babies under two than on older children, but the effects of age and sex have not been studied in any detail. Some division into age groups has been attempted, but a variety of methods of estimation has been adopted and rather variable results obtained, so that before beginning any work on morbid children, it was essential to have a table of normal values, obtained by the same method as that used in the other work.

**NORMAL PERCENTAGE IN ADULTS.**—Taking a review of the literature the normal adult value, as given by different workers, is fairly uniform.

Bloor<sup>1</sup> who quotes the average of figures given in the literature as being 170 mgrm. per cent., gives results which are slightly higher. His own values are 210–240 mgrm. per cent. for women and 190–250 for men. Denis<sup>2</sup> has somewhat similar values: 167–225 for women and 192–255 for men. Chauffard, Laroche and Grigaut give the normal as 150–180, and MacAdam and Shiskin<sup>3</sup> are in close agreement with results of 133–191, the average being 161 mgrm. per cent. Wade<sup>4</sup> also considers the normal value to be 165. Hunt's<sup>5</sup> figures are slightly higher (177 mgrm. per cent.).

**NORMAL PERCENTAGE IN CHILDREN.**—The normal percentages for children quoted in the literature show a very much wider variation. Some of these figures apply to whole blood and others to plasma, which may in part account for some of the discrepancies.

Gordon and Cohn<sup>6</sup>, using Bloor's method on serum, give the average for cord blood as 89; in the first week of life as 87; and afterwards up to two years as 110–190 mgrm. per cent.

Manicattide, Bratesco and Rusesco<sup>7</sup> using Grigaut's method on serum give an average of 131 under four months, and 116 from four months to one year. Their average they took as 125 mgrm. per cent. for all babies whether artificially or breast fed.

Baylac and Sendrail<sup>8</sup> using Grigaut's method on serum give 149 as the average, which is in agreement with Baranski's results of 150 mgrm. per cent. Simone<sup>10</sup> gives values of 67–105, and Varone's<sup>11</sup> results are also rather lower than the average, giving 115 as normal for infants

---

\* Part of a thesis accepted for the M.D. degree, Liverpool University.

under one year, and 137 as the average for children of 2 to 8 years. Dorlencourt and Seitzoff<sup>12</sup> give a higher normal of 140. The results of Gladys Boyd<sup>13</sup> are highest of all. Using Bloor's method she gives a figure of 185 mgrm. per cent.

**Method of estimation.**—Many methods for the estimation of the cholesterol in the blood have been advocated. Probably the most accurate is the digitonin method, but this is difficult of operation and very expensive. The colorimetric methods employed give slightly higher results than the gravimetric, but on the whole they are accurate. In the present investigation, large numbers of estimations had to be performed and a reasonably rapid method was accordingly essential; and as the patients were children, a simple method of obtaining the required small quantity of blood was necessary. The method described by Leiboff<sup>14</sup> appeared to fulfil these stipulations the most conveniently. A small amount of blood only is needed, the apparatus is comparatively simple, and there is very little opportunity for experimental error to occur. The results appear very consistent and thus justify the adoption of this method.

As a preliminary precaution, estimations were made on the writer's own blood, using first a modified Myers-Wardell<sup>15</sup> method and comparing the results obtained by Leiboff's method. The results agreed very well as can be seen in the following list:—

Myers-Wardell method	Estimation 1	156 mgrm. per cent.
" "	" 2	156 " "
" "	" 3	156 " "
Leiboff's method	" 1	153 " "
" "	" 2	155 " "
" "	" 3	169 " "
" "	" 4	155 " "
" "	" 5	160 " "

**Leiboff's method.**—This method is briefly as follows:—

The patient's finger is cleaned thoroughly with ether and pricked. .5 c.cm. of blood can be obtained easily in this manner. .2 c.cm. of this blood is measured out and run on to a specially prepared filter paper thimble end, which is then allowed to dry at room temperature. 5 c.cm. of pure anhydrous chloroform is poured into the extractor tube and the filter paper disc is dropped into position. The tube is attached to a reflux condenser, immersed in a beaker of water, and extraction allowed to proceed for twenty-five minutes. At the end of this time, the extractor tube is removed from the condenser and cooled. The disc is taken out and discarded. Chloroform is now added exactly to the 5 c.cm. mark. In a corresponding extractor tube is poured 5 c.cm. of a standard solution of cholesterin in chloroform, containing .3 mgrm. cholesterin per 5 c.cm. To both tubes are added 2 c.cm. acetic anhydride and .2 c.cm. concentrated sulphuric acid. After mixing and cooling, the tubes are placed in a dark cupboard for twenty minutes. By this time the colour has developed and the contents of the tubes are poured into the cups of a Bausch-Lomb colorimeter and the estimations are made.

**Cases investigated.**—The children chosen to represent the normal, were sound healthy children from an orphanage in the vicinity. They were all leading a normal life of a more or less standardized type, having similar amounts of exercise, diet and school work.

Fifty-nine cases in all were studied, including twenty-six boys and thirty-three girls. All the children were between the ages of thirteen and six years.

TABLE 1.

THE CHOLESTEROL LEVEL IN 59 NORMAL CHILDREN.

Boys		Girls	
Age	Mgrm. per cent.	Age	Mgrm. per cent.
13 years, 8 months	145	13 years, 11 months	137
13 " 6 "	142	13 " 1 "	134
		13 " 0 "	131
12 " 9 "	142	12 " 9 "	136
12 " 0 "	146	12 " 8 "	142
		12 " 8 "	130
		12 " 7 "	158
		12 " 6 "	132
		12 " 2 "	157
		12 " 1 "	157
11 " 11 "	143	11 " 11 "	139
11 " 9 "	145	11 " 10 "	127
11 " 9 "	142	11 " 10 "	135
11 " 1 "	142	11 " 10 "	135
11 " 0 "	140	11 " 10 "	133
		11 " 9 "	128
		11 " 9 "	134
		11 " 5 "	133
		11 " 4 "	125
10 " 9 "	142	10 " 11 "	142
10 " 0 "	142	10 " 5 "	126
10 " 0 "	138	10 " 5 "	125
		10 " 5 "	146
		10 " 4 "	125
		10 " 3 "	137
9 " 10 "	133	9 " 11 "	129
9 " 5 "	132	9 " 9 "	137
		9 " 3 "	142
8 " 11 "	132	8 " 9 "	129
8 " 5 "	136	8 " 2 "	133
8 " 5 "	139	8 " 2 "	129
8 " 4 "	131	8 " 0 "	135
8 " 4 "	131		
7 " 11 "	133		
7 " 11 "	132		
7 " 7 "	136		
7 " 7 "	133		
6 " 11 "	133	6 " 5 "	133
6 " 11 "	130		
6 " 7 "	125		

CHART I.

THE BLOOD CHOLESTEROL OF NORMAL CHILDREN.

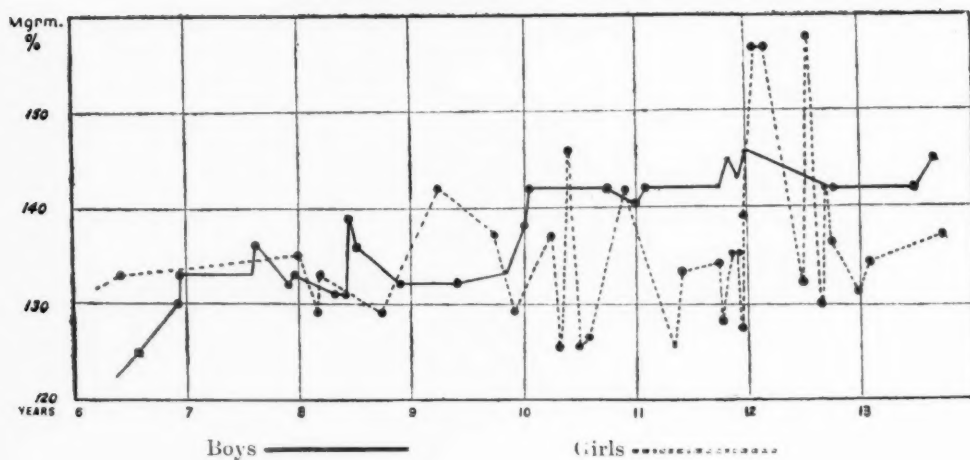
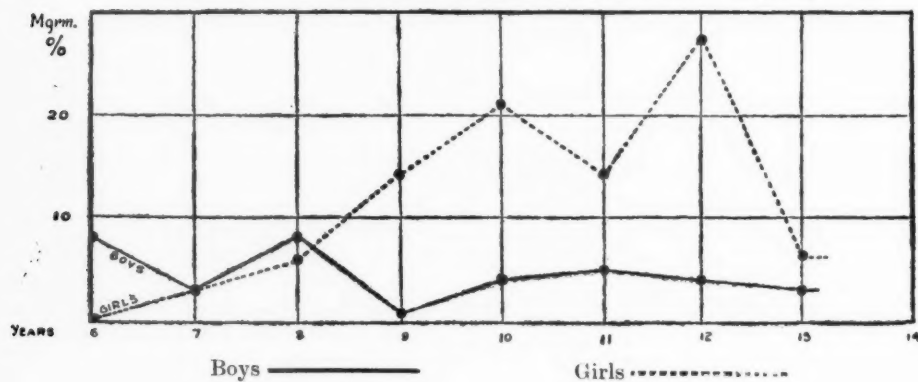


TABLE 2.

AVERAGE BLOOD CHOLESTEROL FOR EACH AGE GROUP.

Boys		Girls	
Age in years	Mgmm. per cent.	Age in years	Mgmm. per cent.
13	144	13	134
12	144	12	145
11	142	11	132
10	140	10	133
9	132	9	136
8	134	8	131
7	134	7	—
6	129	6	133

CHART II.

THE RANGE OF VARIATION AT EACH AGE.  
(max. per cent. cholesterol minus min. per cent. cholesterol).

**Results.**—Table 1 and Chart 1 show the results obtained in each case graduated according to age.

Table 2 shows the average readings of the blood cholesterol for each age group.

**Discussion.**—Table 1 and 2 show the results obtained and for greater ease of explanation these have been expressed in the form of graphs also (Charts I and II). From a consideration of the figures given, some facts of importance emerge.

First, it is obvious that a consistent level of blood cholesterol is maintained throughout childhood. In the case of boys, this shows a steady and progressive rise towards puberty, with a rather more rapid increase from the age of nine onwards. From nine to ten years the curve is steep, but a more even level is maintained from ten to thirteen. In the case of girls the amount of variation at every age is markedly greater than that shown by the boys, and this is especially manifest between the ages of ten and thirteen when a definite degree of instability exists, the curve tending to show a drop at eleven with a subsequent rise at twelve. The whole curve is entirely different from that of the boys, a progressive rise from the time of the second dentition until puberty not being apparent.

A curve of the range of variability has been plotted (Chart II), and this shows very clearly the wide range of variation which occurs in girls, especially at the ages of ten, eleven and twelve. This may be regarded as being coincident with the onset of puberty.

It will be seen also from a consideration of the graphs that the cholesterol level in girls tends on the average to be somewhat lower than in boys at every age.

---

## II. THE BLOOD-CHOLESTEROL LEVEL IN CHILDHOOD DURING DISEASE.

From a consideration of the literature, it is apparent that the blood cholesterol level is disturbed during the course of many diseases.

During the present investigation, many examples of various diseases have been studied, but chief among these have been patients showing various phases of rheumatic infection. The main object in view being to determine whether or not there is any abnormality in the cholesterol content of the blood during the course of juvenile rheumatism, estimations have been made in cases selected from all stages of the disease. It was hoped that this would show some facts of interest. In addition, an attempt was made to correlate the results with obvious foci of sepsis in teeth and tonsils, and also to compare them with a similar series of cases in which leucocyte counts were performed.

TABLE 3.

GROUP A. THE CHOLESTEROL LEVEL IN CHILDREN SUFFERING FROM ACUTE RHEUMATISM.

Sex	Age years	Clinical history	Mgrm. per cent.
Male	9	Vague pains; joints not affected; early carditis; tonsils + and infected ... ..	143
"	9	First attack of chorea; nil cardiac ... ..	146
"	9	Recent acute arthritis; nodules present; nil cardiac; tonsils and teeth healthy ... ..	131
"	6	First attack of chorea; nil cardiac ... ..	125
Female	11	Pains; nil cardiac ... ..	140
"	11	Acute chorea and pains; active recent carditis; tonsils + and septic ... ..	140
"	11	Acute chorea (early); heart nil; tonsils + and septic ... ..	126
"	8	Acute chorea; nil cardiac; tonsils + ... ..	125
"	8	Acute articular rheumatism; nil cardiac ... ..	132
"	8	Rheumatic fever in 1928; acute chorea; nil cardiac ... ..	130
"	8	Acute chorea; nil cardiac; tonsils + ... ..	128

TABLE 4.

GROUP B. THE CHOLESTEROL LEVEL IN CHILDREN SUFFERING FROM CHRONIC RHEUMATISM.

Sex	Age years	Clinical history	Mgrm. per cent.
Male	12	Chronic mitral stenosis: now has acute articular rheumatism ...	136
"	8	Pains and established mitral disease ... ..	150
"	8	Established mitral stenosis, and acute articular rheumatism; tonsils unhealthy; teeth bad ... ..	133
"	6	Established mitral leak; acute articular attack; tonsils + and septic ... ..	154
Female	11	Established mitral stenosis ... ..	184
"	11	Growing pains; established mitral regurgitation; tonsils + ...	144
"	11	Established mitral lesion ... ..	163
"	11	Chronic mitral stenosis ... ..	146
"	10	"Felt tired" for one year; triple mitral bruits; tonsils not +	180
"	10	Recurrent attacks of chorea ... ..	173
"	10	Chorea; established mitral affection ... ..	153
"	9	Recurrent chorea; tonsils + and septic ... ..	140
"	9	Recurrent chorea; nil cardiac; tonsillectomy previously ...	151
"	9	Recurrent rheumatism; nil cardiac; tonsils + and septic ...	150
"	9	Established mitral leak ... ..	144
"	9	Established double mitral and aortic lesions ... ..	155
"	9	Recurrent chorea; heart, ? early infection; tonsils healthy ...	166
"	8	Recurrent arthritis with carditis; tonsils + and unhealthy ...	173
"	8	Recurrent chorea; nil cardiac; teeth septic ... ..	177
"	8	Established mitral stenosis; tonsils + and septic ... ..	146
"	8	Established mitral lesion ... ..	154
"	6	Established mitral regurgitation ... ..	160
"	5	Recurrent chorea; tonsils + and septic ... ..	154

CHART III.

THE BLOOD CHOLESTEROL IN ACUTE AND CHRONIC RHEUMATISM.  
(Average for each age group).

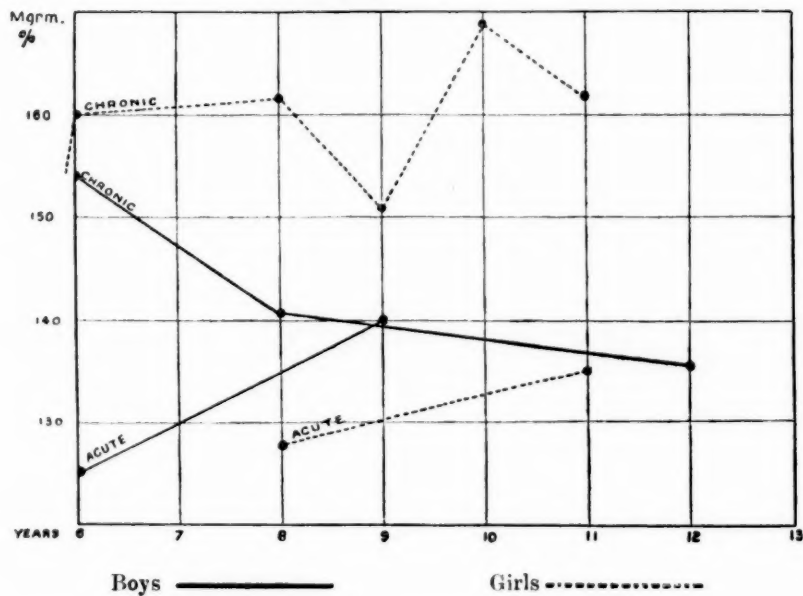


TABLE 5.

THE CHOLESTEROL LEVEL IN CHILDREN SUFFERING FROM VARIOUS DISEASES.

Age years	Sex	Disease	Mgms. per cent.
13	F	Chronic nephritis; œdema +; blood urea + ... ..	165
11	M	Chronic nephritis ... ..	187
11	M	Chronic nephritis; no œdema; blood urea normal ... ..	200
8	F	Chronic nephritis; no œdema; blood urea normal ... ..	132
7	M	Chronic nephritis; no œdema ... ..	155
11	M	Asthma: idiopathic ... ..	148
10	M	Asthma: idiopathic ... ..	140
4	M	Asthma: idiopathic ... ..	130
9	M	Diabetes; no ketosis ... ..	147
10	F	Enlarged tonsils and adenoids ... ..	141
8	M	Enlarged tonsils and adenoids ... ..	174
10	M	Fidgety and nervous; no definite signs ... ..	153
8	F	Dystrophia adiposo-genitalis ... ..	150
12	M	Fragilitas ossium ... ..	150
6	F	Banti's disease ... ..	160
8	M	Chronic lymphatic leukæmia ... ..	160
8	M	Hæmophilia ... ..	Less than 120

This part of the investigation has been carried out on cases of juvenile rheumatism, but as this term embraces such a number of widely differing sets of symptomatology and consequently varied clinical pictures a little classification was necessary. The best division from the point of view of this paper seems to be into two large groups :—

GROUP A.—Recent, acute, active rheumatism including muscular pains, swollen joints, pancarditis and chorea, usually associated with some degree of fever (Table 4).

GROUP B.—Rheumatism of a more chronic type, including recurrent chorea, myocarditis, endocarditis and established valvular lesions. Some of these cases were undergoing a secondary acute relapse and the picture becomes more complicated, but for the sake of clarity and ease of explanation, a short clinical history is appended to each case (Table 5).

In addition to the cases of rheumatic infection, some other diseases have been studied (Table 6). These form a heterogeneous group, including cases of chronic nephritis, idiopathic asthma, chronic lymphatic leukaemia, fragilitas ossium and a few patients with chronic infected tonsils and adenoids. The cases of chronic nephritis were thought to be of interest in view of the increase in blood cholesterol reported in this condition ; and the asthma cases represented specimens of an allergic condition. The cases with septic tonsils were chosen for comparison with cases of rheumatic infection in which similarly infected throats were present.

---

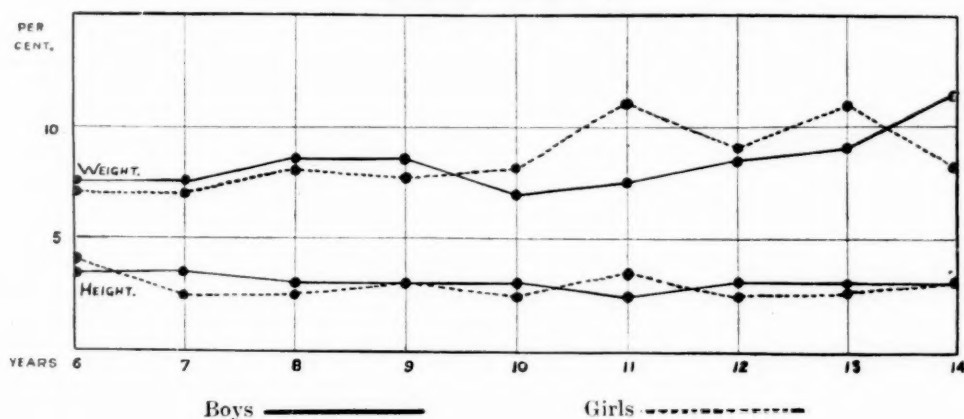
### III. DISCUSSION OF RESULTS.

From a consideration of the known facts of the physiology and pathology of cholesterol in the animal body, it is apparent that a great amount of knowledge is not available upon these points. Conjecture is rife, but solidly established facts are relatively few, and even those known are difficult of correlation into a complete picture and many gaps are left unfilled. As this is the case, to draw sweeping conclusions from the results quoted would be unjustifiable and almost certainly fallacious. Some facts and points of interest do emerge, however, and these will now be considered.

For a full appreciation of these facts, a few observations on the physiology of the child are necessary. That the metabolism of the normal healthy child differs in many essential ways from that of the healthy adult is undoubted. On the whole, the balance of the child's biochemistry is very much more easily influenced by external factors and consequently is much more readily disturbed. The fact that growth is taking place rapidly means that the whole metabolism is in a constantly changing state, anabolism being much more marked than katabolism, although this is taking place to a less degree, and no organ of

the body remains static for any length of time. A review of the growth process is given in Abt's *Pediatrics*<sup>16</sup>. The termination of the infantile and the beginning of the juvenile growth cycle at about the time of weaning is characterized by profound metabolic changes, the infant's body having to adjust itself to an altered diet and consequently to a change of materials for building up new tissues. Again, at the junction of the juvenile and adolescent growth cycles, there is a similar metabolic upheaval, and a relative instability of the growth process is shown. In the investigation quoted by Abt the increase of weight and stature, and the variability of each, in a number of healthy boys and girls was obtained. The boys showed a steady yearly increment of weight and height, while the girls gave a far less steady increment. The variability of weight of the boys, which was not great at any age, was slightly increased at the age of eight and nine years. The girls, showing at all

CHART IV.  
THE VARIABILITY OF HEIGHT AND WEIGHT.  
(from Abt's *Pediatrics*).



ages a more marked variability, accentuated this slightly at the age of eight, but much more so at ten, eleven, twelve and thirteen years. The variability of height was not quite so obvious, and did not appear to affect any one age group more than another. It becomes apparent at once, that the two sexes show a marked difference in their response to the growth process (Chart IV).

Passing on from a consideration of the effect of growth, the basal metabolism may next be discussed. The basal metabolism appears to increase with age during babyhood, reach its maximum at the age of four years, and then fall gradually, reaching the normal adult value at about twenty years. It is a well recognized fact that a relatively high basal metabolism characterizes the period of growth. In this as in the growth process, the influence of sex is marked from early years, it being definitely lower in the female than in the male. Sonden and Tigerstedt (quoted by Abt) found that under like conditions in the young, the carbon dioxide output both per kilogramme of body weight and per square metre of surface, is considerably greater in males than in females,

This difference becomes less apparent with increasing age, until in old age it disappears completely. Benedict and Talbot also state that boys have a higher average metabolism than girls of the same weight.

A consideration of the differences between the blood of the adult and that of the child is illuminating also. At birth the specific gravity of the baby's blood is equal to that of the adult, but thereafter it rapidly becomes less and remains at a lower level, the boys at all ages showing a higher specific gravity than the girls. Feldman<sup>17</sup> considers that the specific gravity is not dependent on the number of corpuscles, but on their hæmoglobin content, and this is low in childhood, rising gradually to the adult level at about puberty.

A further point of difference is the relative numbers of the cells of the blood. These are all greater in the child than in the adult, the red cells averaging 5,800,000 from 1—14 years, and the white cells 10,000—7,000 per c.mm.; also there is a relative lymphocytosis of 30—50 per cent. of all white cells, owing to a greatly increased activity of adenoid tissue in children in which the tonsils, thymus, lymphatic glands and spleen all take part.

As regards the chemical constituents of the blood, the non-protein nitrogen content, comprising urea, uric acid and creatinine are within the same limits as in the adult, but creatine behaves rather differently in the child. Feigl<sup>18</sup> believes that there is a tendency revealed by the averages of his different age groups for the creatine and creatinine of the blood to increase with age from childhood onwards. Fonteyne and Inglebrecht<sup>19</sup>, however, did not discover any relation of age to creatinine, but agreed that it influenced the amount of creatine. Rose<sup>20</sup> showed that children of both sexes excrete creatine in relatively large quantities, and regard creatinuria as a normal accompaniment of the growth process. Rose thought this persisted in both sexes until or even after puberty, but Krause<sup>21</sup> believes that boys cease to excrete creatine at the age of five or six years, while girls usually, but not necessarily always, continue to excrete it for some years longer. He believes that the excretion of creatine is entirely dependent on the balance maintained between its formation and destruction, and that the power of dealing with it is less well developed in the child than in the adult.

From the time of birth onwards the food of the child, consisting as it does mainly of carbohydrates, proteins, fats and salts, is comparable to that of the adult, but the use to which these substances are put differs somewhat. In the adult, protein is broken down and used to repair damage to vital cells, while fats and carbohydrates supply the necessary fuel. It has been shown also, by Cathcart, that carbohydrates are necessary for synthetic processes in the cells in connection with protein metabolism and do not act merely as spacers of protein. In the child, however, anabolism is proceeding rapidly and a source of supply of energy which is easy of obtaining must be at hand. Substance metabolism is usually taken to mean chiefly the metabolism of proteins, since these constitute the essential substrata of living protoplasm. Salts rank next in importance, but fats and carbohydrates are regarded as being merely accessory. Abt considers it doubtful if the attitude of regarding the

fats and carbohydrates merely as fuel is correct. Lipoid matter, which is present in company with the fats, is of great importance structurally, especially in the building up of the nervous system.

From this brief summary of some of the points of difference between the metabolism of child and adult it is seen that the numerous factors taking part in the growth process seem to be responsible and that these appear to behave rather differently in the case of the boys than in that of the girls.

Some curves are reproduced (Chart 4) from Abt's work on pædiatrics showing the variability of growth and height at different ages in boys and girls and from these it is seen at a glance that the variation in height is not marked at any age in either sex, but that there is an increased variability in the weight curve, which is much more evident in the case of the girls. It is interesting to compare this curve with that already given as indicating the variability of blood cholesterol at different ages.

In both of the latter curves the variations are rather more accentuated than in the case of the growth curves, but here again the girls show a wider range, and in each case this appears to show more at a year earlier than in the growth curve. For example, the two peaks of the growth variation are at eleven and thirteen years, while those of cholesterol variation are at ten and twelve years. It seems not unlikely that there may be a relationship between the two, and that this is not merely accidental, cholesterol possibly playing some important part in the process of growth. Further confirmation of this view is found in the work of Shope<sup>22</sup> in America. He states that a number of investigators have surmised that differences in blood-cholesterol level occur in organisms of various ages and differing stages of development. Roffo<sup>23</sup> experimenting on rats found that the blood cholesterol increased between three and five months of age, Baker and Carrel<sup>24</sup> using chickens found a marked difference with age. Shope used for his investigations cattle, rabbits and guinea pigs all of varying ages. He found the variations with age to be of two types:— (a) a marked and rapid increase from birth, lasting throughout the early life of the animal; and (b) a less marked but more gradual decline with advancing age. In all cases he found the changes in cholesterol content of the blood to be more uniform and regular in male than in female animals. In female guinea pigs, the blood cholesterol showed many irregular fluctuations which in many cases were unrelated to age, and Shope questions whether possibly cholesterol serves more functions in the female organism than in the male. These fluctuations are, in the case of female children fully confirmed in the present investigation, but their exact interpretation is not possible at the present stage of our knowledge of the functions of cholesterol in the body.

Passing on from the normal figures given, it is necessary to say a few words about the rheumatism curves, and the figures obtained from cases of other diseases. Here again, the results are not easy of interpretation. From Table 3 (Group A) it may be concluded that during the more acute phases of rheumatism, the blood cholesterol is not greatly disturbed. In the first two cases in Table 3 the figures are perhaps slightly higher than normal, but on the average the figures are within normal limits and do not show much variation,

Turning to the results in the chronic rheumatism group (Table 4) very different figures are found. The general trend is for an average higher than the normal for any age, in many cases this being very marked. Cases having an acute attack superimposed on a chronic cardiac lesion show a lower cholesterol level than those with uncomplicated heart disease. No direct association with infected teeth or tonsils could be traced, some cases with chronic sepsis showing an increase in cholesterol and others none, but in this connection it is interesting to note that a case of chronically infected tonsils, without any rheumatic symptoms did give a very high result.

Kipp<sup>25</sup> during his studies of pneumonia traced a relationship between the number of leucocytes in the blood and its cholesterol content, and in the present investigation many leucocyte counts were performed, but no parallelism could be made out. The average counts in both the acute and chronic cases of rheumatism were between the limits of 6,000 and 12,000 cells per c.mm. in a few cases rising to 15,000 per c.mm., but as has been stated already the normal may be regarded as lying between 7,000 and 10,000 per c.mm. so that these counts show a very mild grade of leucocytosis, and this did not appear to bear any relationship to the increased cholesterol in the more chronic cases. The hæmoglobin content of the blood also has been thought to have an influence on the cholesterol content, but here again explanations break down, as many of these children have a marked secondary anæmia.

The most reasonable explanation which can be put forward at the present time with the amount of knowledge at our disposal is that of the growth process again. It is a well known fact that during the course of chronic juvenile rheumatism growth is much impeded, the children being thinner than normal and often under the average in size, and it may be suggested that possibly the excess of cholesterol in the blood would in the normal course play some part in anabolism, but that the disorganization of the growth process by the rheumatic condition leads to a slight degree of accumulation in the blood.

There is less interest attached to a consideration of Table 6 which comprises a group of cases suffering from fairly common diseases. Included in this series are five cases of chronic nephritis, one of which showed marked œdema. In four out of the five cases a greatly increased blood cholesterol was found, one case giving as much as 200 mgrm. per cent., which was the highest reading recorded in the whole investigation. Three cases of idiopathic asthma, one of diabetes without ketosis, and one of chronically infected tonsils and adenoids, yielded normal results. Two cases of dystrophia adiposo-genitalis gave results rather higher than normal, as did a case of Banti's disease and one of chronic lymphatic leukæmia. A single case of hæmophilia gave a result which was too weak to estimate with the usual standard solution used in the colorimeter, and was therefore less than 120 mgrm. per cent. The child, aged eight, was having a fairly severe hæmorrhage at the time the investigation was made.

No explanation of these results is attempted at the present time, but they are recorded, being of interest in that they confirm the results already published in the literature,

### General conclusions.

Estimations of the blood cholesterol of children of both sexes between the ages of six and thirteen lead to the following conclusions :—

1. The average percentage of blood cholesterol in healthy boys increases as the age increases and the percentage in individual boys does not differ greatly from the average for that age.
2. The average blood cholesterol of healthy girls increases much less with age than that of healthy boys, and the percentage of cholesterol in individual cases often departs widely from the average for that age.
3. In acute juvenile rheumatism the average percentage of cholesterol in the blood is normal, but in chronic rheumatism it shows a definite tendency to be greater than normal. It is suggested tentatively that this abnormally high level is related to the disordered growth which frequently attends chronic juvenile rheumatism.
4. During the course of the parenchymatous type of chronic nephritis in children, the blood cholesterol rises, as in adults.
5. The blood cholesterol is normal in idiopathic asthma and in diabetes which is being controlled by insulin.

In conclusion, I wish to express my thanks to Dr. Dingwall Fordyce and to Professor Ramsden for much valuable criticism and advice.

### REFERENCES.

1. Bloor, W. R., *J. Biol. Chem.*, Baltimore, 1916, XXV, 577.
2. Denis, W., *Ibid.*, 1917, XXIX, 93.
3. Macadam, W., & Shiskin, C., *Quart. J. Med.*, Oxford, 1922-1923, XVI, 193.
4. Wade, P. A., *Am. J. Med. Sc.*, Philadelphia, 1929, CLXXVII, 790.
5. Hunt, H. M., *New England J. Med.*, Boston, 1929, CCI, 659.
6. Gordon, M. B., & Cohn, D. J., *Am. J. Dis. Child.*, Chicago, 1928, XXXVI, 192.
7. Manicatide, M., Bratesco, A., & Rusesco, A., *Compt. rend. Soc. de biol.*, Paris, 1927, XCVI, 1240.
8. Baylac, J., & Sendrail, M., *Bull. et mem. Soc. méd. d. hôp. de Paris*, Paris, 1928, LII, 33.
9. Baranski, quoted by Baylac & Sendrail, *vide supra*.
10. Simone, quoted by Baylac & Sendrail, *vide supra*.
11. Varone, L., *Riv. di Clin. pédiat.*, 1929, XXVII, 599.
12. Dorlencourt, H., & Seisoff, C., *Bull. Soc. de pédiat. de Paris*, Paris, 1929, XXVII, 352.
13. Boyd, G., *Am. J. Dis. Child.*, Chicago, 1929, XXXVIII, 490.
14. Leiboff, S. L., *J. Biol. Chem.*, Baltimore, 1924, LXI, 177.

15. Myers, V. C., & Wardell, E. L., *Ibid.*, 1918, XXXVI, 147.
16. Abt's *Pediatrics*, 1924, I.
17. Feldman, W. M., *Antenatal & Postnatal Child Physiology*, London, 1920.
18. Feigl, J., *Arch. f. Exp. Path. u. Pharmak.*, Leipsic, 1918, LXXXIII, 335.
19. Fonteyne, P., & Inglebricht, P., *Ann. de méd.*, Paris, 1923, XIV, 470.
20. Rose, W. C., *J. Biol. Chem.*, Baltimore, 1911-1912, X, 265.
21. Krause, quoted in Hunter's *Creatine & Creatinine*.
22. Shope, R. E., *J. Biol. Chem.*, Baltimore, 1928, LXXX, 141.
23. Roffo, A. H., *Compt. rend. Acad. d. sc.*, Paris, 1925, CLXXX, 1529.
24. Baker, L. E., & Carrel, A., *J. Exp. Med.*, N.Y., 1927, XLV, 305.
25. Kipp, H. A., *J. Biol. Chem.*, Baltimore, 1920, XLIII, 413.

# GANGRENE IN AN INFANT ASSOCIATED WITH TEMPORARY DIABETES

BY

R. D. LAWRENCE, M.A., M.D., M.R.C.P.,

and

R. A. McCANCE, M.A., M.D., M.R.C.P., Ph.D.

(From King's College Hospital, London.)

Gangrene and diabetes are both extremely rare in the first few weeks of life. Still more unusual are the cure of the gangrene and the complete disappearance of the diabetes. We propose in this paper first to place on record and discuss such a case, and secondly to review the recorded cases of diabetes in children under one year of age.

## Report of authors' case.

The clinical record of our case is as follows :—

A female infant of 18 days was admitted to King's College Hospital on 12th March, 1931, under Dr. Still. Four bluish-black patches were present in different parts of the skin and the child was obviously extremely ill.

She was the first child of healthy parents, born at full time after a normal labour in which instruments were used. Her birth weight was 7 lb. 14 oz. She was breast fed every three hours, but took rather little milk. The stools were somewhat more green than normal, but the child seemed to be perfectly well and, when the nurse left at the 12th day, had regained exactly her birth weight.

On the 15th day a black patch was noticed on the flexor aspect of the right wrist, and that night and the next the child slept poorly and was disinclined for food, but seemed otherwise well. On the 17th evening a black mark was seen on the dorsum of the left ankle, and next day two other blue patches were noticed, one extensive on the right hip. The child was brought to hospital and admitted in the early evening.

On admission her temperature was 96.8°, pulse 160, and respirations 44 per minute. The child looked wasted, the skin was loose and inelastic, the weight only 5 lb. 7 oz., so that a rapid loss had taken place in a few days. On the right hip, just over the trochanter, was a large round purple-black patch (5 by 4.5 cm.) with a dark red margin, neither raised nor very indurated. There were smaller similar oblong patches on the right wrist and left ankle. Nothing abnormal was found on general examination elsewhere, although the child was evidently extremely ill.

The child was fed every 2½ hours on Nestlé's milk (1 part in 10 water) with lactose added, so that the diet contained 18–20 gm. carbohydrate per day. Brandy, 2 minims, was added to alternate feeds.

13th March. A fresh blue patch (2 by 2 cm.) appeared on the other hip just over the trochanter. It was clear that the gangrenous area over each trochanter had developed at pressure points, and the black areas on the wrist and ankle were probably also subjected to pressure as the child lay with its limbs folded over each other. Temperature was 98-99°, pulse 160 and respirations 44 per minute. The child seemed desperately ill although she took her feeds. The brandy was omitted and sherry whey given as alternate feeds to the Nestlé's

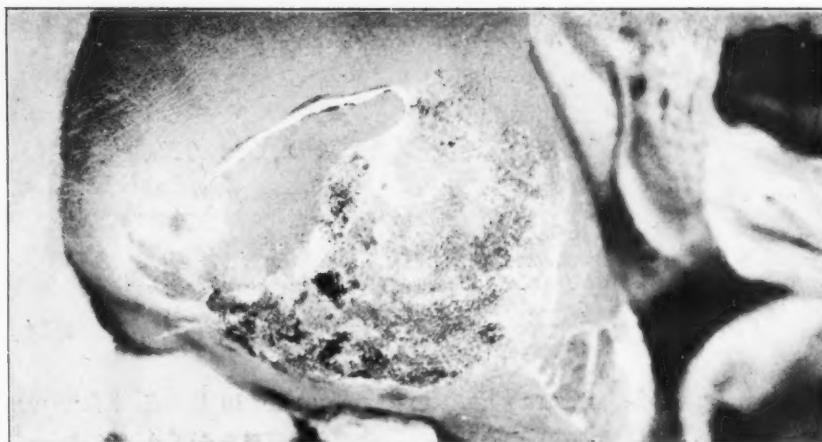


FIG. 1. 20th March. Gangrenous area just breaking down.



FIG. 2. 16th July. Gangrenous area completely healed for 6 weeks. Note the increased fatness.

mixture. The stools were dark with undigested curd. No diagnosis was made, but 10 c.cm. of polyvalent antistreptococcal serum were given.

Late that night the first specimen of urine was obtained and found to be loaded with sugar, but to contain no acetone bodies.

14th March. The urine from the preceding night was found to contain 4.2 per cent. of

sugar, no ketone bodies, but on boiling a heavy cloud of albumin. Microscopically a few leucocytes, but no red blood corpuscles or casts were detected. The blood-sugar was approximately 0.6 per cent. As these tests demonstrated diabetes, insulin, 1 unit every 4 hours, was commenced and the same diet continued. The child seemed much weaker with a pulse of 166 (approximately) and a temperature of 100° F.

15th March. Qualitatively the urine contained less, but still considerable amounts of sugar. On account of the gangrenous areas, it was considered inadvisable to hold the child over a vessel to obtain specimens and it was extremely difficult to collect more than a few drops of urine to test for sugar. One unit of insulin was continued four-hourly and the same feeding. The general condition seemed desperate. The temperature rose to 103°, the pulse rate remained about 160, but the respirations at times rose to 80 per minute. Frequent jerking nystagmoid movements of the eyes to the right were observed, but the fundi appeared normal. The patches on both hips were now definitely gangrenous, of a dull dark slate colour with red inflammatory edges, the whole area feeling brawny.

16th March. The urine still contained a large amount of albumin but only a trace of sugar (about 0.2 per cent.), and a few white blood corpuscles and granular casts with many oxalate crystals were observed in the deposit. Insulin was reduced to half a unit four-hourly. The baby's respirations were steadier and the nystagmoid movements less obvious. The child was so weak that it had to be fed by a pipette every hour.

17th March. The sugar in the urine was reduced to the merest traces and accordingly insulin was reduced to  $\frac{1}{2}$ -unit morning and evening. The child was extremely feeble, but no further extension of the gangrenous areas had taken place.

18th March. As the reducing substance in the urine still amounted to only the merest trace,  $\frac{1}{2}$ -unit of insulin was given in the morning. This was the last dose the child received. It was thought that the slight trace of 'glycosuria' might be lactose, which was being added to the feeds. Sufficient urine to test this was never obtained. As no more than traces of 'sugar' appeared subsequently in the urine, further insulin was deemed unnecessary.

19-28th March. The temperature gradually fell from 103° to 100° in this period, and the child slowly improved and gained 5 oz. The gangrenous areas on both hips slowly separated and weak wet cusol dressings were substituted for powder. The last trace of reducing substance disappeared from the urine on the 21st March and never appeared again. Minute traces of protein were excreted for another fortnight. The diet was changed to a Cow and Gate milk feed suitable for a normal child of its age.

Normal diet was continued and at the end of May the child was discharged apparently normal in every respect and gaining 4 oz. a week. A dose of glucose (1½ grm. per kgrm. of weight) was substituted for an ordinary feed and no glycosuria resulted. By the end of June the largest gangrenous area had completely healed, the urine was entirely normal, and the blood-sugar concentration 1 hour after a feed was 0.058 per cent., a low normal figure.

Figures 1 and 2 are from photographs of the largest gangrenous area before and after healing.

SUMMARY.—An infant who had previously made normal progress developed four black skin areas, two frankly gangrenous, between the 15th and 18th days after birth. At the same time an acute and severe form of diabetes developed and no general infection or disease of the central nervous system was discovered to account for the hyperglycaemia. The diabetes responded to insulin treatment, rapidly disappeared, and remained absent when the insulin was discontinued. The gangrene healed slowly in 11 weeks. The child was discharged from hospital normal in every way.

### Case records of infantile diabetes.

Cases of diabetes in infants under twelve months are very rare and the recorded cases have never been collected or discussed in the British literature. In 1913 Knox<sup>20</sup> searched the medical records from 1852 to 1913 and published

in America 16 cases (including one of his own) which appeared to him to be examples of true diabetes mellitus. He dismissed 11 others which had been reported as diabetic, because the evidence was not conclusive. Since then no complete collection of cases has been made in the literature of any country.

Within the last decade our knowledge of diabetes has been extended and the criteria of diagnosis have become more exacting. Besides glycosuria, hyperglycæmia and ketonuria (whether absent or present) are now considered essential details of any records of adult diabetes. These are still frequently unavailable or omitted in records of infantile diabetes, and the diagnosis often rests on symptomatology and the presence of glycosuria. These latter, if very definite, may be accepted as clearly establishing the diagnosis, especially if the usual fatal issue is recorded and no other cause of death is found.

In our critical review of the literature we have accepted infantile diabetes as proven in cases :—

1. Where definite wasting, thirst, polyuria and preferably ketonuria were present, accompanied by a heavy glycosuria (over 2 per cent.), whether the reducing substance was actually proved to be glucose or not, even if hyperglycæmia was not established ; or

2. Where, if the symptoms and glycosuria were slight, definite and recurrent hyperglycæmia (over 0.2 per cent.) was established.

We have classed as non-diabetic :—

1. Cases which show only one or two symptoms suggestive of diabetes, in which the glycosuria was only slight and might be due either to lactosuria (not infrequent in infants) or to renal glycosuria, a low renal threshold, which is as common in children as in adults in our experience ; and

2. Cases in Group 2 above in which hyperglycæmia is present, but in which it is never excessive (i.e., under 0.3 per cent.), and which may be explained by temporary infection or disease of the central nervous system, such as trauma, tuberculous meningitis or hydrocephalus (Harrison<sup>13</sup>).

Adopting the above criteria, we give a short description of all the cases so far recorded arranged in chronological order. Some doubtful cases are mentioned : these not described fully and are marked with an asterisk. General features are discussed later.

Haüner<sup>14</sup> (1850) reported the first authentic case in an infant of 11 months. The child became thin and thirsty and passed 7 to 9 litres of 'sweet urine' per day. It died in coma one month later.

Kitselle<sup>15</sup> (1852) recorded another case soon after. A male child (his own son) plump and strong at birth, developed a few days later symptoms of diabetes. 'Honeyed' napkins were first noted, then polyuria with sugar was found on the 14th day. The child was restless, thirsty, hungry, and dry skin and extreme emaciation developed. It survived for 6 months, a living skeleton, being fed on breast milk, bread and water and semmel tea. The urinary tract then became infected and the child died. No mention is made of hereditary or causal factors.

Rosbach<sup>16</sup> (1874) described a female child of 7 months, previously healthy, who had a severe fall on the head, followed by convulsions and unconsciousness. A month later thirst, polyuria, furunculosis and wasting became obvious. The glycosuria varied from 2 to 10 per cent. and, although feeding with broths, cream and diluted milk diminished the sugar, she died in extreme

emaciation 3 months after the accident. No family history is recorded and, although a post-mortem examination was made, the pancreas was not examined. This is not surprising as the connection between the pancreas and diabetes was only discovered in 1889.

Busch<sup>6</sup> (1876) records a case 'under a year' who became restless, thin, and very thirsty. A glycosuria of 5 per cent. was discovered, and the child died in coma 23 days later.

Hagenbach<sup>12</sup> (1879) reports the case of a male infant who developed thirst and polyuria at 8 months. At 10 months a heavy glycosuria was found and hydrocephalus noticed. He was fed with milk, dosed with salicylic acid, and died 11 months later. At autopsy gangrene of lungs, tuberculous pleurisy on the right side, and oedema of the pia mater with chronic internal hydrocephalus were found.

\*Garnerus<sup>11</sup> (1884) published the case of a male child entitled, 'Cure of Diabetes Mellitus and Inspidus in an Infant.' Polyuria (sp. gr. 1008-10) was noted almost from birth and some sugar (? glucose) found at the 2nd month. The sugar disappeared later, but polyuria (sp. gr. 1000) remained. We do not consider even temporary diabetes proven in this case.

Nichues<sup>31</sup> (1891) records that a male infant of 3 months, whose grandfather died of diabetes, developed abscesses and polyuria. 3 per cent. of sugar was found in the urine and the child soon died.

Tavaria<sup>37</sup> (1893) reports a case of a Parsee child (sex unstated) who, previously in perfect health, fell out of its cradle at 10 months, but sustained no visible injuries. It became restless, and developed a fever of 103°, for which no cause was found. It passed urine 2-3 times per hour, was very thirsty and crowds of flies were noticed round the napkins. A large amount of sugar was found ('about one-third'), and the child became very weak, but not emaciated. Two weeks later it developed pneumonia and died in coma. The author blames a 'nervous cause' as responsible.

Bell<sup>5</sup> (1896) was called to attend a well-nourished male child of 3 months, who had developed thirst and genital irritation one month before. He found much sugar in the urine and eczema of the thighs. Nutrition was good and constipation absent. The baby was fed on its mother's milk (she being put on a diabetic diet!) and given unlimited skimmed milk and water for its excessive thirst. It died in coma 4 days later and the post-mortem examination showed nothing abnormal macroscopically. The father's aunt had died of diabetes.

\*Baumel<sup>4</sup> (1900) reports that a female infant with no diabetic family history developed at 6 months oedema, itching, hunger and polyuria ('urine like water,' sp. gr. not stated). Traces of 'sugar,' never more than 0.150 per cent. were found in the urine, but the reducing substance was never proved to be glucose. The child continued breast feeding, received a few medicaments (including extract of lily of the valley!) and the oedema and glycosuria disappeared in 6 weeks. Whether the polyuria and thirst disappeared simultaneously is not mentioned. To our mind no proof of diabetes mellitus is given in these records.

Orloff<sup>32</sup> (1901) records a case of a male of 5 months who developed restlessness, thirst, polyuria, boils and a sacral sore. Glucose was found in his urine and the polyuria was excessive. He wasted rapidly and died in a few days. Hydrocephalus, especially of the lateral ventricles, was found and also bronchopneumonia and acute enteritis.

Young<sup>39</sup> (1902) describes a male foundling of 6 months whose illness began with vomiting, dryness of the skin, emaciation, enlarged kidneys and liver. 5 per cent. of sugar, albumin, and a few casts were found in the urine. He was given pasteurized milk and codein which had no effect. He lived one month and died of pneumonia. Post-mortem the kidneys were twice the normal size, the cortex indurated, the parenchyma inflamed and also the mucous membrane of the bladder. The liver also was enlarged, but nothing else abnormal was discovered.

Langstein<sup>24</sup> (1909) describes three cases:—

\*1. A six months' child with severe chronic hydrocephalus developed a glycosuria varying from 0.1 to 1 per cent., irrespective of diet, but showed no symptoms of diabetes. At death extreme hydrocephalus and thinning of brain were confirmed.

\*2. An anencephalic child showed 0.5-1 per cent. of sugar in the urine from the 7th to 10th day, when it died. It had no diabetic symptoms.

3. A male child of 8 months developed symptoms of diabetes, dry skin, thirst, hunger, loss of weight. There was no family history of diabetes, but the child had been overfed from the sixth month with large excess of sugar and milk, receiving about 200 gm. carbohydrate per day. He was put on a milk mixture containing 40 gm. carbohydrate and excreted 10-6 per cent. of sugar, but no acetone (total excretion not stated). He was then fed on a 'sugar-free' milk containing only 8 gm. carbohydrate, and excreted 8 gm. of glucose per day. On this diet a heavy ketosis and early signs of coma appeared which cleared up with sodium bicarbonate and two 'oatmeal days.' Later the diet consisted of 'sugar-free' milk, whey, some oatmeal and broth and spinach (quantities not stated) on which the glycosuria disappeared. When this diet was increased, sugar reappeared in the urine. On this restricted diet the weight and clinical condition remained stationary for some months, but the ultimate fate of the child is not mentioned.

Lauritzen<sup>25</sup> (1910) mentions a boy of 8 months with large amounts of sugar and ketone bodies in his urine who died in coma 3 months later.

Eaton and Woods<sup>9</sup> (1911) describe their case in a healthy breast-fed baby weighing 16½ lb. at 6 months. The parents were normal, but one grandmother had died of diabetes. Delivery was instrumental and the baby suffered a large superficial cut over the left eye, but the head seemed normal later and the baby made excellent progress until the 6th month. Then one toe became red and swollen and a vesicle developed on it and a week later a toe of the other foot became the same. Next thirst, wasting and sticky napkins were noticed, and 6-10 per cent. of sugar and 'acetone but no diacetic acid' were found in the urine. The baby was fed on breast milk and given 'trypsinogen' which was not found beneficial; later washed cream and beef-juice were given. Glycosuria was always present, but Knox states that the child lived for two years longer.

\*Cuno<sup>7</sup> (1911). A 15 day old marasmic child (weight 2,800 gm.) was found to have 0.3 per cent. glycosuria. It died in a week from bronchopneumonia and post mortem had an abnormally small pancreas (1.5 gm.) showing cirrhotic changes which he considered congenital. Not a clear case of diabetes.

Knox<sup>20</sup> (1913) describes his case in an 8 months' female child in considerable detail. There was no family history of diabetes and the baby was fairly healthy till 5½ months and the urine was known to be sugar free, as it had been examined occasionally for previous slight pyuria. After some slight digestive upset, she received for a time a large amount of malt soup (10 per cent.) in her milk. This was stopped and the child did well for another month, when loss of weight, dry skin and a fruity odour in the breath led to the discovery of 5 per cent. of glucose and some acetone in the urine. Slight fever (99-100°) was present for a few days. 'Eiweiss milk-cream' mixture was given, whereupon the glycosuria diminished to 1.5 and later to 0.6 per cent., but in about a week drowsiness, nausea and air hunger developed and, in spite of treatment by bicarbonate and fluids, she died in coma with a rising temperature and bronchopneumonia. The post-mortem reports on the pancreas are given later.

Kochmann<sup>21</sup> (1922) described the first child (birth weight 2,500 gm.) of healthy parents who at 4½ months became very thin and tired and developed intertrigo. Sugar (5-9 per cent.) was found in the urine, but no acetone. On reduced diet the sugar fell to 1-2 per cent. At that time the blood sugar fasting was 0.095, but rose after food to 0.387 per cent. Just before death the fasting blood sugar was 0.444 per cent. This is the first case of infantile diabetes in which determinations of blood sugar were made. On special diet there were only traces of sugar in the urine. When taking the average amount of milk for its age, the child put on weight, but excreted more sugar. An oatmeal 'cure' had also this effect. At 6½ months it developed fever and died in coma from confluent hæmorrhagic bronchopneumonia. The autopsy is described later.

Ashby<sup>3</sup> (1923). A child of 5 months developed slight pyelitis and fever. The urine does not seem to have been tested for sugar at this time, but soon gangrene of two toes developed and then glycosuria was found. The child died some weeks later and was almost comatose 3 days before death.

Major and Curran<sup>28</sup> (1915) describe the case of a male child of 11 months, who was admitted to hospital for glycosuria of 1 month's duration. The blood sugar varied between 0.094 and 0.222

per cent. A family history of diabetes was negative. A diet of whole milk, vegetables and cod liver oil was given and insulin 6-10 units per day. Cataracts had already developed in both lenses, which were extracted and found not to be congenital. One year later the insulin was stopped, but glycosuria returned. 2 to 3 units a day were found necessary. We do not know the further history, but presumably the child's condition required the continued use of insulin.

Schippers<sup>35</sup> (1925). A girl of 8 months old, the 3rd child of healthy parents, developed a temperature of 102°; 9.1 per cent. of sugar and much acetone were found in the urine as well as protein, casts and white blood corpuscles. Insulin, 5 units, b.d., was given. The temperature became normal in 5 days and the casts disappeared. A typical day's food consisted of milk 200 grm., cream 50 grm., butter 3.7 grm., potato 100 grm., vegetable 100 grm., apple 150 grm. (= 46 grm. carbohydrate, 17 grm. protein and 54 grm. fat). She progressed for many months on 8 or 9 units of insulin b.d. Suddenly at the age of 2 years 2 months she became ill, vomited and could not be fed. Insulin and carbohydrate were given as much as possible, but she died in coma 2 days later.

De Lange<sup>8</sup> reports the autopsy on this case which we shall deal with later.

Arndt and Welcher<sup>2</sup> (1926) describe a case of considerable interest in a child of 3 months with no diabetic heredity. It weighed 2,000 grm. at birth and gained on the breast for 4 weeks, although passing 4 or 5 loose motions a day. At 10 weeks it seemed weak and tired and on admission to hospital was pale and very poorly nourished, with oedema of the eyelids and over the tibiae. The physical examination revealed nothing else abnormal. The urine was strongly positive to Trommer's test, but otherwise normal. The blood count showed a secondary anaemia; red blood corpuscles, 2,570,000 per c.mm., Hb. 58 per cent. The child took its food well (8-900 grm. of mother's milk) and the weight and oedema remained constant. The urine (sp. gr. 1.005) contained 0.8 to 1 per cent. glucose, but no acetone; and the motions, 4-6 a day, were loose, clear gold colour, contained mucus, but were not 'shiny'. The fasting blood sugar was .257, and 1 and 2 hours after food it was .275 and .299 per cent. respectively, clearly diabetic. No symptoms of diabetes were present. The Wassermann test was negative. No change occurred during 7 days in the clinic until 4 units of insulin were given. No definite signs of hypoglycaemia were observed, but 10 hours later the oedema increased and death occurred from heart failure.

The autopsy (details given later) showed much greater defect in the alveolar than islet tissue, and we presume that this as well as the diabetes contributed to the marasmus.

Ramsey<sup>33</sup> (1927) describes the case of a full term male, delivered naturally, who had a family history of diabetes, but 5 brothers and sisters alive and well. The birth weight was 2,200 grm., at 18 days 2,200 grm., and at 4 weeks 2,085 grm. Then the child developed slight fever, catarrh of the upper respiratory tract, polydipsia, polyphagia and polyuria, and was found to have a heavy glycosuria. In hospital he lost ground on breast milk and protein milk (140 cal. per kgrm.) and  $\frac{1}{2}$ -unit of insulin (? how often) made him sugar-free on the 4th day. The insulin was discontinued twice, but on each occasion sugar reappeared in the urine. The blood sugar was 0.225 per cent. but the time relation of this test to food is not stated. Finally, after 18 days insulin he kept sugar-free on whole lactic milk. When syrup was added, sugar returned with a blood sugar of 0.263, which fell to 0.750 per cent. on omission of the syrup. He was discharged from hospital in 6 weeks on 600 c.cm. whole acid milk (120 cal. per kgrm.) and remained sugar-free except when syrup was given experimentally 3 and 6 weeks later. At 7 months he was in excellent health (wt. = 7,900 grm.), and the urine was sugar-free on a diet of whole milk, cream of wheat, vegetables, orange juice and cod liver oil—practically normal.

By the courtesy of Dr. F. G. Hedenstrom, of St. Paul, Minnesota, we are able to give details of the child at 4 years of age. A blood-sugar curve with glucose (amount not stated) gave the following completely normal results:—

Fasting ...	...	...	...	...	0.060 per cent.
After 1 hour	...	...	...	...	0.095 "
„ 2 hours	...	...	...	...	0.082 "
„ 3 „	...	...	...	...	0.077 "
„ 4 „	...	...	...	...	0.074 "

We gather that the child is perfectly well on a normal diet. Dr. Hedenstrom particularly states that polyphagia and polydipsia were present before the initial catarrh, so that the diabetes was not caused, but only accentuated, by this infection. In this case the presence of true diabetes with subsequent recovery is clearly established.

Lenstrup<sup>26</sup> (1928) mentions a child of 11 months doing well on insulin, but gives no details.

Morton<sup>29</sup> (1928) reports the case of a male child of 12 months whose paternal grandfather had diabetic gangrene. The infant had gained rapidly till the 12th month, when it became fretful, lost weight and developed hunger, thirst and polyuria. The urine was loaded with sugar and diacetic acid. It was given 12 units of insulin, b.d., with a diet equivalent to 74 gm. glucose and 62 gm. fatty acids, and soon developed symptoms of insulin overdosage. A month later 6 units of insulin, b.d., controlled the diabetes on a diet of 28 gm. carbohydrate, 27 gm. protein and 56 gm. fat. At 2 years the child weighed 25 lb. and less insulin was needed to keep it well and practically aglycosuric.

Joslin<sup>17</sup> (1928) describes a male infant, with a family history of diabetes, who developed diabetes at 8 months. He was fed on a nearly normal diet varying from 73 gm. carbohydrate at 10 months to 100 gm. at 2 years, supplying about 100 calories per kgrm. In these two years the insulin increased from 12 to 18 units a day, given in three doses, and the urine remained sugar-free. The child kept well and its weight, although subnormal, increased satisfactorily.

Litchfield<sup>27</sup> (1930). A male child, 5 months old, developed a napkin rash shortly after its breast feeding was supplemented by cane sugar and cereals. Its birth and early months had been normal and there was no history of diabetes in the family. At 7½ months 6.6 per cent. of sugar was found in the urine which was reduced to 4.3 on breast feeding alone. Slight ketonuria was present, the blood sugar was 0.420 per cent. and insulin (15–10–15 units) was started. Hypoglycæmia developed and recurred on 10 units b.d. When insulin was stopped the rash and 6.8 per cent. of urinary sugar recurred. Finally the child was given 5 and 7 units per day and kept in excellent condition.

Shelley<sup>36</sup> (1931) reports the case of a child who was perfectly well till the 8th month. Labour was normal and a family history of diabetes absent. At the 8th month 'chill and fever' occurred for a few days and again for 4 days during the 9th month. At the 10th month polydipsia, polyuria and irritation of the skin developed, the napkins were noticed to be sticky and at the 11th month 2 per cent. of sugar and traces of acetone were found in the urine. The blood sugar was 259 mgrm. per 100 c.cm. The Wassermann and Pirquet tests were negative. A normal diet and 3 units of insulin, t.d.s., were given and the blood sugar is recorded as 327 mgrm., the urine sugar 1 per cent.; 5 units t.d.s. made the urine sugar-free for a few days, but the blood sugar varied between 240 and 280 mgrm. per 100 c.cm.—evidence of a high renal threshold. After 10 days the child went home and continued to improve on diet and insulin: but polyuria, polydipsia and polyphagia were always worse when insulin was omitted. At 15 months it developed acute fever with diarrhoea and vomiting, epidemic at that time. It died in two days, and an autopsy was not obtained.

### Congenital diabetes.

In only two of the above cases is there any probability that the child was born a diabetic. Three other cases are recorded as congenital diabetes and will now be considered.

Ambard et al.<sup>1</sup> (1925) describe the case of a child born of a diabetic mother at the 8½ month of intra-uterine life. The mother was precomatose and was treated with large doses of insulin (up to 180 units a day). On the day when labour was induced the maternal blood sugar was 0.44 per cent., but had fallen to 0.180 next day when the mother died (blood urea—0.163 per cent.). At birth the sugar in the umbilical cord blood (? artery or vein) was 0.242 and in the placental blood 0.228 per cent. The infant lived only 21 hours and the urine collected from the 11–15th hours contained 1.2 per cent. of sugar, the presence of ketone bodies not being mentioned. Autopsy showed abnormalities (cloudy and hydropic degeneration) of the maternal

islets, but normal islets in the infant, although the acinar tissue looked cirrhotic and infiltrated with lymphocytes.

The authors claim that the infant was diabetic, but we consider this not proven. It did not live long enough to disprove the possibility that its hyperglycaemia and glycosuria were due entirely to the maternal diabetes.

Feldman<sup>10</sup> (1928) reports as congenital diabetes a still more doubtful case. A woman of 32, in the ninth month of her pregnancy, was admitted to hospital after one day of unconsciousness, and died 2 hours later from heart failure. Post mortem, sugar and ketone bodies were found in the urine, and histologically the islets of Langerhans were diminished in number and size, and their cells showed 'destruction' and cloudy swelling. The urine of the unborn child contained more sugar than that of the mother, but no ketone bodies. Histologically the child's pancreas showed many enlarged islets, and oedema and dropsical swelling of the cells.

In this case diabetes was not proved, even in the mother, although it is the best explanation of her death and the urinary findings. This would easily explain the foetal glycosuria and, as we shall see later, little attention can be paid to theories built on the histological appearance of the islets, on which Feldman's arguments rest.

Nevinny and Schretter<sup>30</sup> (1930) describe a more interesting case very completely. The mother was obviously a mild diabetic in whom thirst and neuritis appeared 3 months before her 8th pregnancy. Her glycosuria was readily controlled by diet and the blood sugar records towards the end of pregnancy varied between 157 and 67 mgrm. per 100 c.cm., not clearly diabetic. However, during a febrile attack 10 days after labour, her blood sugar rose to 324 mgrm. and insulin was required for a few days, so that definite diabetes was present.

The child, born 12 days after the reckoned time, weighed 4,750 gm. Her previous children weighed about 6 kgrm. The following interesting series of blood sugars were obtained at birth; amniotic fluid 161, maternal venous blood 104, retro-placental blood 89, umbilical vein 87, and umbilical artery 62 mgrm. per 100 c.cm. Obviously the child was not diabetic at birth, its blood sugar being lower than the mother's. One of us (R. D. L.) has found this relationship present in 4 cases of children of diabetic mothers.

The child lived 29 days and died with marked cyanosis, due to congenital heart disease, confirmed at autopsy. Its capillary blood was frequently tested for sugar. At birth, 62; at 5½ hours, 52; 2nd day, 52; 5th, 62; 8th, 106; 12th, 95; 15th, 172; 22nd, 162 mgrm. The time of these tests in relation to food is not stated. No glycosuria and no symptoms of diabetes were present.

At autopsy the pancreas was macroscopically normal although perhaps somewhat heavier than the average at one month. The islets were more numerous than in controls of the same age and large hypertrophic islets ('Riesensinseln') were much more frequent than usual. The other endocrine glands were normal except for an enlargement of the anterior lobe of the pituitary which was exceptionally rich in eosinophil cells.

The authors conclude from the hypertrophy of the islets and the rising blood sugar that the infant had an 'overwork diabetes' (überarbeitungsdiabetes). In our opinion the histological picture is the opposite of diabetic and it is possible that the slightly rising blood sugar may have been produced by the child's circulatory failure, and especially the cyanosis. Asphyxia is known to elevate the blood sugar and might afford an explanation of the only feature in this child suggesting diabetes. Whether chronic cyanosis in an infant can elevate the blood sugar we do not know: it is a point which does not seem to have been investigated.

**Conclusion.**—On the available evidence we do not think any case of congenital diabetes proven in medical records.

### Post-mortem reports on the pancreas.

In only five of the above cases was any histological examination of the pancreas made, and very little exact information is available on the normal appearance of the infantile pancreas with which to compare these records.

In older children, evidence of lesions of the islets is frequently entirely absent and less commonly obtained than in adults. In 22 children Warren<sup>38</sup> found the histology of the pancreas entirely normal in 12, and readers are referred to his recent book for further detail. The main histological features in the above cases will now be described.

Heiberg<sup>15</sup> describes the post-mortem appearances in a child of 14 years who had developed the disease at about 1 year old and died in coma. The islet cells were mostly normal, the islets themselves were perhaps rather small. Some round-celled infiltration was present in the islets and surrounding interstitial tissue. Heiberg counted the number of islets per 50 c.mm. and found them reduced in number to 58 instead of the normal 200-300. Such enumeration, however, is generally agreed to be difficult and of little value (see Warren).

Knox's<sup>20</sup> case showed a pancreas which was normal macroscopically. Sections of the pancreas showed the lobules to be separated from each other by rather broad septa, which consisted principally of very loose connective tissue. There were many small round cells in the interstitial tissue which in some places seemed to replace the acini. The connective tissue was increased. The islets were diminished in size and number. In one section none were seen.

Kochmann's<sup>21</sup> case showed fatty changes in the acinous cells and there were very few islets. Considerable generalized lymphocytic infiltration was seen. A small cyst was present in the middle lobe of the pituitary.

De Lange<sup>8</sup> made a very careful examination of Schipper's case. Nothing really abnormal was found in the number, size or histological detail of the islets. The liver contained much glycogen.

Arndt and Welcher<sup>2</sup> found a generalized anaemia, a diffusely fatty liver, but a normal pancreas macroscopically. On section the pancreatic parenchyma (acini) was widely infiltrated with fat, leaving the islets rather conspicuous. The islets were mostly increased in size and normal in appearance, although some small-celled infiltration was present. They state that the number of islets was diminished (218 per 50 c.mm.), but in comparison with Heiberg's figures this does not seem to us to be true. Certainly the main histological feature was acinous atrophy although, from the blood-sugar results, islet function was also involved. A congenital maldevelopment of the pancreas seems probable in this case, and the symptomatology due more to failure of external than internal pancreatic function.

**Conclusion.**—We feel that these reports do not help us to associate failure of insular function with any constant histological picture. The only characteristic appearance regularly noted is a round-celled infiltration which Warren describes as perhaps the only characteristic lesion of the islands in older children. He states that it is 'obviously not a primary lesion,' but suggests a reaction to some toxic substance or to the necrosis of the islet cells produced by overstrain.

### General discussion.

We may now proceed to a general discussion of our own and other recorded cases.

**1. Incidence.**—**SEX.** This would appear to be overwhelmingly male. Of the cases where the sex has been stated 17 have been male and only 7 female. In 5 cases the sex is not mentioned.

**AGE.** Of the cases of proved diabetes, 7 have been recorded between the 9th and 12th months of life, and exactly the same number between the 6th, and 9th months and between the 3rd and 6th months. Below three months however, only 3 cases have been recorded—all in the first few weeks of life—and of these 2 have recovered. The third which was one of the earliest ever recorded (Kitselle<sup>19</sup>) lived for 6 months and might conceivably have recovered under modern methods of treatment. The available evidence therefore suggests that, while over 3 months the disease resembles the adult type, temporary loss of islet function may occur in the very early days of life.

**2. Symptoms and signs.**—These do not differ materially from those of older children and adults. The onset and course have almost always been very acute, which is the usual form of diabetes in older children. Restlessness and slight fever seem more common initial symptoms than they are in adults, but these are the disturbances which characterize so many childish complaints that little diagnostic significance can be attached to them. Sticky napkins seem to have attracted the attention in many instances. Genital irritation and napkin rashes are naturally more frequent.

Gangrene and pre-gangrenous changes were noted in two other cases besides our own (Ashby<sup>3</sup>, and Eaton and Woods<sup>9</sup>). In older children and young adults these signs are practically unknown and in elderly diabetics are essentially due to concomitant arterial degeneration. In infants it must be presumed that the nutritional disturbance of severe diabetes, acute in our case, may produce gangrene apart from arterial disease.

**3. Aetiology.**—**INFLUENCE OF HEREDITY.** In 12 cases no mention is made of a family history of diabetes, either positive or negative. Of the remainder 35 per cent. had a family history of diabetes, which is higher than the figures generally given for diabetes of all ages, but lower than those of the private cases of one of us (R. D. L.). Von Noorden thought that hereditary influences were less important in children than in adults, but Joslin's cases point to the opposite conclusion. It is probable, therefore, that the hereditary factor in infants is of similar importance to that in adults.

**NERVOUS INFLUENCES.** Falls on the head have preceded the onset of two of the cases (Tavaria<sup>37</sup> and Rosbach<sup>34</sup>), and in the one described by Rosbach the association of the injury with the onset is very striking. Hydrocephalus has been associated with three of the cases reported (and anencephalus with one), although those of Langstein<sup>24</sup> hardly conform to our criteria of true diabetes. The diabetes, indeed, in these cases is generally mild and a secondary factor in the fatal result.

**INFLUENCE OF OVERFEEDING.** This appears to have been a contributory factor in a few cases (Langstein<sup>24</sup>, Knox<sup>20</sup>) where the child has been forced to take large amounts of sugars, starches and malt extracts. Such cases do not appear before the 6th to 9th month, but it is evident from the number of children who are fed on very similar lines that the overfeeding can only have been a contributory factor.

**PANCREATIC DISEASE.**—Generalized pancreatic inflammation and cirrhosis seem to have been responsible for two cases (Arndt and Welcher<sup>2</sup>, Cuno<sup>7</sup>). Cuno's case was not definitely diabetic, but mild glycosuria was associated with generalized pancreatic cirrhosis, and in the case recorded by Arndt and Welcher the external disorder of the gland was probably the main cause of death.

It is evident that, as in so many cases of adult diabetes, the aetiology of infantile diabetes remains obscure.

**4. Treatment and prognosis.**—Before the use of insulin, death was the inevitable issue. Few cases survived the diagnosis by more than a very few months. Most lapsed into coma, but a few succumbed to infections, such as pneumonia. Reduction of the carbohydrate of the diet, by modifying the milk and so on, may have reduced the glycosuria, but made no difference to the fatal issue. Many of the cases, however, since insulin was introduced have not only lived, but thriven. No doubt the care of such a child is exacting, but good results are assured if the parents and physician are skilled and careful. Milk must and should form the basis of the diet and is relatively much lower in the ratio of carbohydrate (5) to protein (3.5) and fat (3.5) than the mixed diets of elder children and adults. The easy and rational treatment therefore is to give the infant a normal diet for its age and enough insulin to balance it. Babies are fortunately not upset by insulin injections, and two, or probably three, small doses a day give the best results. If complete control is attempted by two larger doses a day hypoglycaemia will probably ensue. As insulin has been available for less than 10 years and so far case records are rare, it is not possible to dogmatize on the future of these children; but there is no evidence at present why they should not grow up normally as older diabetic children have done.

**RECOVERIES.**—Apart from our own case, only one complete recovery has been recorded (Ramsey<sup>33</sup>) in infantile diabetes. Garnerus<sup>11</sup> and Baumel's<sup>4</sup> cases, where recovery was claimed, do not seem to us to have been proved cases of diabetes. A very few cases of recovery in older children have been reported (Joslin<sup>18</sup>), but as evidence of hyperglycaemia was not supplied in these cases, one feels somewhat dubious about their true nature. 'Cures' in adult diabetes are also poorly substantiated, although great improvement in carbohydrate tolerance is common in the early months of treatment. Joslin hardly believes in the possibility of a genuine and complete recovery of normal carbohydrate tolerance. This makes the question legitimate whether the two reported cases were truly diabetic. We feel that the evidence on this point in Ramsey's<sup>33</sup> case is absolutely definite and, in our own, permits of no other conclusion. Wasting, glycosuria (4.2 per cent.) and extreme hyperglycaemia (0.6 per cent.) were all present, and also, as no other cause for the gangrene was discovered, we have regarded it as secondary to the upset of carbohydrate metabolism. What disorganized the islet function so completely and yet so reversibly must remain mere conjecture. No infection or intracranial lesion was ever found to account for the hyperglycaemia.

La Barre and Hoet have shown by different experiments that the secretion of insulin is, partially at least, under the control of the vagus nerves, but we have no reason to suppose that any vagal dysfunction was present in this child. Whatever the cause it was evidently quickly removed.

We conclude that the islet tissue, perhaps because it was quickly protected from overstrain by the exogenous insulin, was able to recover from its disorganization and resume its function.

### Summary.

1. A case of gangrene associated with acute diabetes mellitus is reported in an infant of 18 days. Treatment with insulin resulted in a cure of the gangrene and complete recovery from the diabetes.
2. The medical literature from 1850 to the present day has been searched for cases of diabetes in infants under one year of age. Twenty-six true cases, including our own, are described and discussed. In two complete recovery is established.

---

We are indebted to Dr. G. F. Still for the opportunity to treat and record this case : also to Dr. Snowball, the house physician, and Sister Edith for their arduous attention to the child. We also thank the Medical Research Council for part-time grants.

---

### REFERENCES.

1. Ambard, L. et al., *Soc. méd. d. Hôp. de Paris*, Paris, 1925, XLIX, 3s., 547.
2. Arndt, H. J., & Welcher, A., *Ztschr. f. Kinderh.*, Berlin, 1926, XLI, 518.
3. Ashby, H., *Lancet*, London, 1923, i, 22.
4. Baumel, M. L., *C.R. XIII cong. internat. de méd.*, Paris, 1900 (*Sect. méd. de l'enf.*), 627.
5. Bell, W. B., *Edinb. Med. J.*, Edinb., 1896, XLI, 709.
6. Busch, *Jahresb. u. d. Fortschr. d. Med.*, Berlin, 1876, II, 271 ; cited by Stern, C. *Arch f. Kinderh.*, Stuttgart, 1890, XI, 103.
7. Cuno, F., *Ztschr. f. Kinderh.*, Berlin, *Referate*, 1912, i, 191.
8. De Lange, C., *Am. J. Dis. Child.*, Chicago, 1926, XXI, 840.
9. Eaton, P. J., & Woods, E. B., *Tr. Am. Ped. Soc.*, Chic., 1911, XXIII, 244.

10. Feldman, I., *Centralbl. f. allg. Path. u. path. Anat.*, Jena, 1928, XLII, 435.
11. Garnerus, H., *Deutsche med. Wchnschr.*, Leipsic, 1884, X, 697.
12. Hagenbach, *Jahrb. f. Kinderh.*, Leipsic, 1879, XIII, 421.
13. Harrison, G. A., *Dis. of Child.*, (Garrod, Batten, Thursfield & Paterson), Lond., 1929, 2nd Ed., 535.
14. Häüner, *Wchnschr. f. d. ges. Heilkunde*, Berlin, 1850, XXI, 321.
15. Heiberg, K. A., *Arch. f. Kinderh.*, Stuttgart, 1911, LVI, 1911.
16. Hoet, J. P., & Debois, G., *Compt. rend. Soc. de Biol.*, Paris, 1930, CIII, 516.
17. Joslin, E. P., *Treatm. of Diabetes Mell.*, Philad., 1928, 4th Ed., 838.
18. Joslin, E. P., *Loc. cit.*, 148 & 188.
19. Kitselle, J. f. *Kinderh.*, Leipsic, 1852, XVIII, 313.
20. Knox, J. H. M., *Bull. Johns Hopkins Hosp.*, Baltimore, 1913, XXIV, 274.
21. Kochmann, R., *Jahrb. f. Kinderh.*, Berlin, 1922, XCIX, 20.
22. La Barre, J., *Arch. internat. de physiol.*, Liège, 1927, XXIX, 227.
23. La Barre, J., *Compt. rend. soc. Biol.*, Paris, 1928, XCIX, 1053.
24. Langstein, L., *Verhandl. d. kong. f. inn. Med.*, Wiesb., 1909, XXVI, 209.
25. Lauritzen, M., *Arch. de méd. d'enf.*, Paris, 1910, XIII, 561.
26. Lenstrup, E., *Klin. Wchnschr.*, Berlin, 1929, VIII, 2244.
27. Litchfield, H. R., & Shermer, B., *Ped. Bull.*, Baltimore, 1930, I, 5.
28. Major, R. H., & Curran, E. J., *J. Am. Med. Ass.*, Chicago, 1925, LXXXIV, 674.
29. Morton, H. B., *Nebraska Med. J.*, Lincoln, 1928, XIII, 9.
30. Nevinny, H., & Schretter, G., *Arch. f. Gynak.*, Berlin, 1930, CXL, 396; CXLIII, 465.
31. Nichues, F., cited by Wegeli, E., *Arch. f. Kinderh.*, Stuttgart, 1896, XIX, 8.
32. Orloff, M. N., *Abs. Semaine méd.*, Paris, 1901, XXI, 192.
33. Ramsey, W. R., *Tr. Am. Ped. Soc.*, Chicago, 1926, XXXVIII, 100.
34. Rosbach, T., *Berl. Klin. Wchnschr.*, Berlin, 1874, II, 258.
35. Schippers, J. C., *Am. J. Dis. Child.*, Chicago, 1925, XXX, 336.
36. Shelley, E. G., *Pennsylvania Med. J.*, Harrisburg, 1931, XXXIV, 256.
37. Tavaría, H. K., *Ind. Med. Chir. Rev.*, Bombay, 1893, I, 402.
38. Warren, S., *Pathology of Diabetes Mell.*, Philad., 1930.
39. Young, W. E., *Arch. Ped.*, N.Y., 1901, XVIII, 198.

# THE MULTIPLE PUNCTURE CUTANEOUS TUBERCULIN TEST

BY

W. S. CRAIG, B.Sc., M.B., Ch.B.,

Late House-physician, Royal Hospital for Sick Children, Edinburgh.

At a recent meeting of the National Association for the Prevention of Tuberculosis, a special plea was put forward for a wholesale examination of children of school age, with a view to discovering signs of existing latent tuberculous infection. There was general agreement that in such a routine examination the tuberculin test must play an important part, and it is the purpose of this paper to describe a technique for cutaneous tuberculin tests which, in virtue of its speedy application without sacrifice of reliability, appears particularly suited to the requirements of such extensive investigations.

In 1916, a tuberculin skin sensitization test known as the tattoo method was described<sup>1, 2</sup>, which consisted in making a series of small punctures with a sterilized sewing needle through a film of pure old tuberculin placed on the previously cleansed skin. The tuberculin was afterwards wiped off and the test read in 48 hours. There was a distinct appeal in the rapidity of the above tattoo method, but the repetition of skin punctures appeared to involve an unnecessary amount of physical discomfort and mental strain on the patient's part. With a view to avoiding these disadvantages while still adhering to the fundamentals of the technique, we used an ordinary three-pronged vaccinator, applying it twice, and exactly in the way described for the needle in the above method. In all, 50 cases were subjected to the tuberculin cutaneous test: (a) using the vaccinator, and (b) using the modified Pirquet test as described by McNeil<sup>3</sup>.

The results of the two methods corresponded exactly, suggesting that the use of the vaccinator involved no loss of reliability.

At best, the use of the vaccinator was but an extempore effort, and it was felt desirable to aim at a method which by one application would affect the necessary number of skin punctures, and at the same time involve a test area constant in form and dimensions. Accordingly the instrument and technique described below were devised, and the method carried out over a series of 612 cases.

**Technique of method.**—The instrument (Fig. 1) consists of a handle (A), five needles (B), and a protective cap (C). The needles are so arranged that when the long axis of the instrument is held at an angle of  $30^\circ$  to the plane of the skin, the points of the two longest (a and a<sup>1</sup>) and of the two shortest (b and b<sup>1</sup>) form the corners of a square on the skin plane, the point of needle (c) representing the exact centre of that square.

The method of use consists of the following steps: First, a small area of skin, preferably on the flexor aspect of the arm, is cleansed with methylated

ether. Then with the flat tapered end of the handle, a drop of old tuberculin is transferred from the bottle to the cleansed surface.

With the instrument held as in Fig. 2, the handle at an angle of  $30^\circ$  to the skin surface and the needle points resting on the portion of skin covered with tuberculin, pressure is applied at right angles to the plane of the test area. As pressure, which should be firm and deliberate, is applied, the points of the needles (all five at the same time) are felt to penetrate the superficial layers of the skin.

Again in a direction at right angles to the skin surface, the needle points are withdrawn, this time with a quick rapid motion, in doing which a distinct catch is felt as the superficial skin layers are passed through.

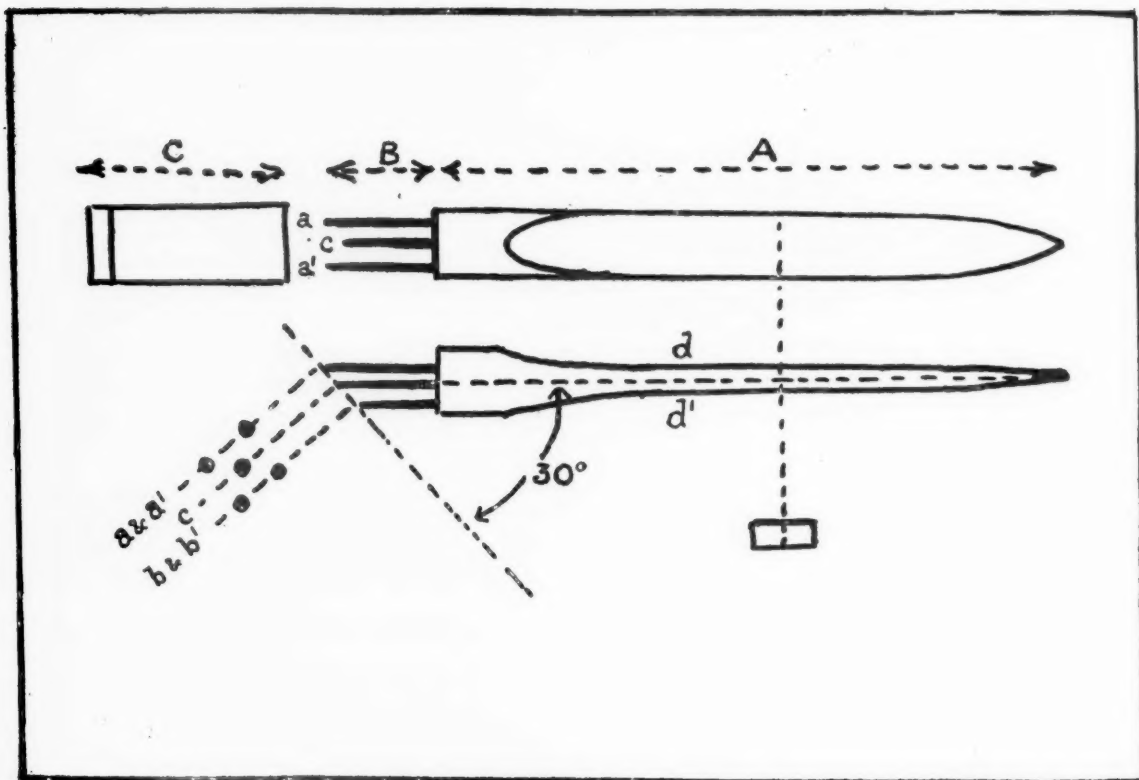


FIG. 1. Cutaneous tuberculin test instrument used in multiple puncture method. (Actual size).

It requires but one successful performance of the test to appreciate the sensation of adequate penetration and the catch on withdrawal, and these are of importance as affording very reliable indications as to whether the necessary amount of pressure has been applied. Blood is not drawn.

Finally, the excess of old tuberculin is wiped off.

Reactions are read daily for seven days.

**The nature of the reactions.**—Positive reactions of various types were found to occur differing in (a) form, (b) colour, and (c) size.

(a) If examined early enough the reaction was seen to take the form of five small red papules which, in the matter of hours, fused to give one large

raised circular nodule. In many instances this was the maximum reaction. In other cases the nodule became both more raised and extended, always preserving its symmetrical shape, while in the more violent reaction there appeared also a peripheral zone of erythema. Four cases occurred in which the erythematous zone showed continuity with a mild ascending lymphangitis.

What was taken to be the most severe reaction was found in six children. Twenty-four hours after showing an enlarged red nodule, a small white vesicle arose at each puncture point and proceeded to extend in area until the five vesicles became contiguous without actually coalescing. At this stage, around the vesicular cluster the margin of the original nodule remained as a vivid

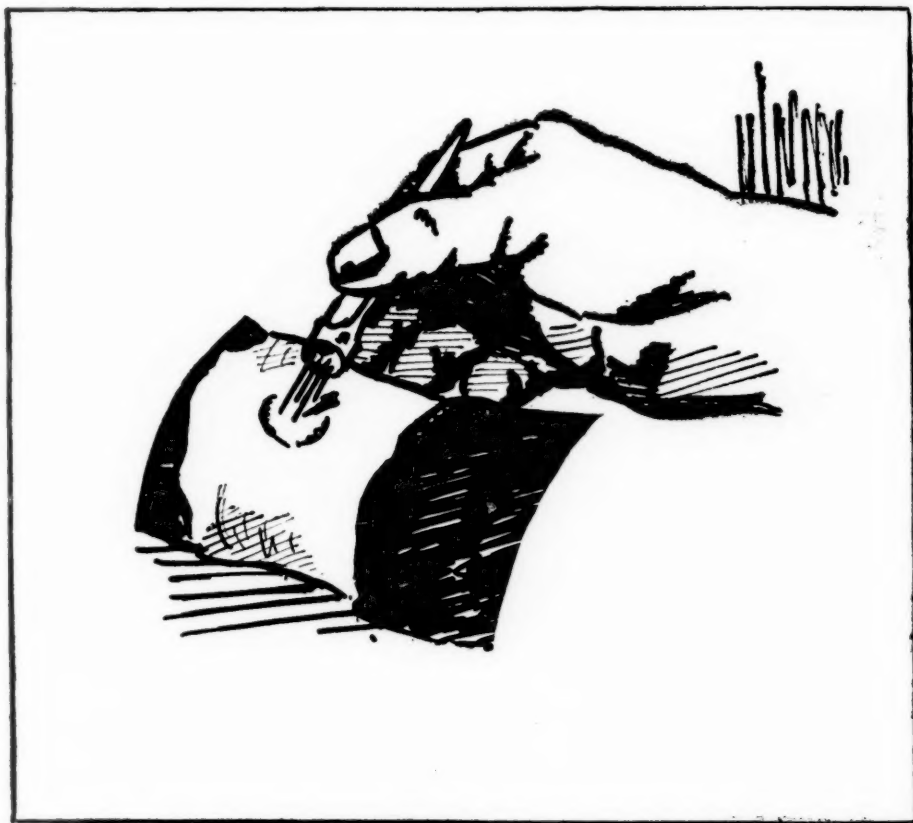


FIG. 2. Cutaneous tuberculin test : multiple puncture method.

boundary line, while outside it again there was a very broad erythematous area.

The weakest type of reaction was met with in two cases of generalized tuberculosis and one of tuberculous meningitis, the tests in each instance having been applied 72 hours before death. In these a cyanotic area became evident, raised to an extent appreciable to light touch only.

(b) With the exception of the weakest positive exactions already described, red was the characteristic colour. The degree of the reaction varied, and although always violent in the most extensive reactions, there appeared to be no exact connection between the area covered by the final nodule and the intensity of the redness.

(c) The diameter of the nodule varied from 10 to 25 mm. In the most violent reactions where a peripheral erythema was present, the erythematous band measured from 3 to 38 mm. giving corresponding over-all diameters of 19 to 57 mm.

No sloughing, systemic or focal reactions occurred in any of the positively reacting children, but of eleven adults tested, all of whom showed a positive reaction, three complained of a slight headache, and one, in addition, of transient nausea.

TABLE 1.  
RESULTS OF TUBERCULIN TEST IN 612 CHILDREN IN AGE GROUPS.

Age in years	No. of tests	Positive reactions	Percentage
Under 1 .. ..	87	15	17.7
1 and under 3 ..	135	36	26.7
3 .. " 5 ..	123	49	39.8
5 .. " 7 ..	104	43	41.3
7 .. " 11 ..	143	65	45.6
11 up to 12 .. ..	20	14	70.0
Total .. ..	612	222	

TABLE 2.  
NATURE OF 612 CASES TESTED.

Medical	Surgical
Lung conditions .. .. 119	Glandular conditions .. .. 17
Abdominal conditions .. .. 48	Bone conditions .. .. 35
Urinary .. .. 29	Joint conditions .. .. 42
Intracranial .. .. 41	Abdominal emergencies .. .. 64
Rheumatic, congenital heart, rickets, feeding, functional, syphilitic and other miscellaneous conditions .. 99	Accidents, scalds .. .. 53
	Poliomyelitis, congenital, sarcomatous conditions, herniæ and other miscellaneous conditions .. .. 65
Total .. .. 336	Total .. .. 276

**Times of reactions.**—Except in the cases of outpatients all arms tested were examined daily for a period of ten days unless the case was previously discharged or died. No single case, other than several of those terminating fatally, was under observation for less than seven days. It was found that in a total of 222 positive results, a definite reaction was present in 196 within 24 hours, in 20 there was no reaction for 48 hours, in two for 72 hours, and only one was delayed for 96 hours before appearing.

**Material investigated.**—The tuberculin test, as outlined above, was carried out over a period of 3½ months on all children admitted to the Royal Edinburgh Sick Children's Hospital irrespective of the age of the child, or whether the case was medical or surgical in nature. Over the entire series of 612 cases, all tests were carried out and read by one observer; Tables 1 and 2 illustrate the type of children embraced by the investigation.

### Results.

In an endeavour to assess the value of the method, investigations were carried out along the following lines :—

1. The reliability of the proposed method (i) as compared with the Pirquet and Mantoux tests ; (ii) as borne out by post-mortem findings ; and (iii) as seen in cases of clinical tuberculosis, in cases of massive tuberculosis, and in cases of high fever.

2. The necessity or otherwise of using (a) a control solution ; (b) bovine and/or human tuberculin.

3. The ease or otherwise of performance.

**Comparison with the Pirquet test.**—In 350 consecutive cases the method under trial was carried out on the left arm while the modified Pirquet test<sup>s</sup> was performed on the other arm. Positive reactions occurred in both left and right arm in 125 cases. In one instance the Pirquet test gave only a dubious positive result while the multiple puncture method showed a definite reaction, and in another case there was no reaction in the latter method although the Pirquet test was positive. Repetition gave positive reactions to both tests in each instance.

**Comparison with the Mantoux test.**—In 50 instances the Mantoux test was carried out on cases previously subjected to the multiple puncture test and the results of the two methods tallied in all cases. Twelve positive reactions occurred in the series of 50, and in the 38 cases showing no reaction either to the proposed method or the Mantoux test with a 1 in 1,000 dilution of old tuberculin, the Mantoux test was repeated using a 1 in 100 concentration without producing any hitherto unrevealed reactions.

**Comparison with post-mortem findings.**—Autopsies were carried out in 90 cases which had been subjected to the test during life and evidence of tuberculous infection was demonstrated in each of the 34 instances where a positive tuberculin reaction had been obtained. Included in these 34 cases were two in which no clinical evidence of tuberculosis had been found. One was a patient admitted on account of extensive burns, in whom were discovered calcified and caseous mediastinal glands with a fibrosis of the upper lobe of the right lung. The other was clinically a case of right lobar pneumonia in an infant of six months : autopsy confirmed this, but revealed also cavitation in the left upper lobe and caseous thoracic glands.

In one single instance was tuberculous infection demonstrated in a case which had failed to react positively to the tuberculin test. This exception occurred in a boy suffering from acute streptococcal meningitis : in a moribund condition at the time of admission, he died without regaining consciousness 36 hours after performance of the test. Post mortem several mesenteric glands were found, judged to be tuberculous on their macroscopic appearance.

**Results in clinical tuberculosis.**—On their discharge the diagnoses of all cases under test were reviewed and the corresponding tuberculin reaction noted to assess the reliability of the method employed in cases of clinical tuberculosis. The term 'clinical tuberculosis' was taken to imply that the presence of Koch's bacillus had been proved, or that some pathological focus directly attributable to a tuberculous infection had been demonstrated.

TABLE 3.  
CASES OF CLINICAL TUBERCULOSIS SUBMITTED TO TEST.

Medical						Surgical					
Meningitis	..	..	..	..	22	Cervical adenitis	..	..	..	..	14
Pulmonary	..	..	..	..	14	Mesenteric adenitis	..	..	..	..	2
Abdominal	..	..	..	..	14	Chronic osteomyelitis	..	..	..	..	1
Generalized tuberculosis	..	..	..	..	4	Chronic osteomyelitis of spine	..	..	..	..	3
Pleural effusion	..	..	..	..	8	Arthritis	..	..	..	..	9
Urinary	..	..	..	..	2	Fæcal fistula	..	..	..	..	10
Total	..	..	..	..	64	Total	..	..	..	..	39

In the series of 612 children, 64 medical and 39 surgical were associated with a clinical diagnosis of tuberculosis, and Table 3 shows the relative frequency of the various conditions.

A positive tuberculin reaction was obtained in all surgical and in 63 of the medical cases. The one exception occurred in a boy with tuberculous broncho-pneumonia, removed from hospital 24 hours after the test had been carried out. At the time of removal a faint localized reddening was present over the test area, but there was no accompanying nodularity so that a positive result could not be claimed during the period of observation.

On the other hand, a number of cases were sent into hospital diagnosed as tuberculous, or subsequent to admission tentatively considered as such, but had the diagnosis revised before discharge. Such cases are shown in Table 4. In all of these the tuberculin test was carried out at least twice, with negative results each time.

**Results in massive tuberculosis.**—In Table 5 are tabulated the results of observations carried out on tuberculous cases which ended fatally, and on which post-mortem examinations were carried out.

Including the examples given in Table 5, the test was applied to a total number of 22 cases of meningitis and 14 cases of pulmonary infection, clinically

TABLE 4.  
RESULT OF TEST IN DOUBTFUL CASES.

Original diagnosis	Final diagnosis	Test
Tuberculous abdomen.	Constipation.	Negative
“ “	†Chronic volvulus	“
Tuberculous ischio-rectal abscess.	†Mixed infection, non-tuberculous	“
Cerebellar tuberculoma (2).	†Megaloblastoma (2).	“
Tuberculous meningitis	Polioencephalitis.	“
“ “	Encephalitis.	“
“ “	*Diabetes mellitus.	“
“ “	Apical pneumonia.	“
Pulmonary tuberculosis (2).	*Broncho-pneumonia (2).	“
“ “	*Aleukæmic leukæmia.	“
Tuberculous glands (2).	†Appendicitis (2).	“

† Operation. \* P.M.

tuberculous. In each of these a positive reaction occurred, with the exception of the one boy already referred to in the previous section.

**Repetition of the test and its value in cases of high fever.**—In 100 cases which had shown no reaction, the test was repeated a second time on the 7th day, and in 30 cases a third time on the 12th day after the first application. Included in these 100 cases were 45 suffering from lobar pneumonia, and in them the test was performed within four hours of admission when the condition was at its height, while the second test was applied when the temperature had fallen to, and remained normal, for a minimum period of three days.

In no case did repetition produce a positive result.

TABLE 5  
RESULTS OF TEST IN MASSIVE TUBERCULOSIS.

No.	Pathological diagnosis	Test result	Test days before death
1	Miliary tuberculosis with meningitis .. .. .	++	4
2	Terminal .. .. .	++	3
3	Generalized tuberculosis .. .. .	+	15
4	Tuberculous meningitis .. .. .	++	14
5	" .. .. .	+	5
6	" .. with acute miliary tuberculosis ..	Faint	3
7	Abdominal tuberculosis .. .. .	+++	3
8	Acute tuberculous broncho-pneumonia .. .. .	Faint	1½
9	Tuberculous meningitis .. .. .	+++	21
10	" .. .. .	++	7
11	" .. .. .	++	7
12	Miliary tuberculosis with meningitis .. .. .	+	1½
13	Tuberculous meningitis .. .. .	+	10
14	" .. .. .	+	1½
15	" .. with limited miliary spread ..	+	4
16	" .. .. .	+++	3
17	Alveolar pneumonia with latent pulmonary tuberculosis ..	+	5
18	Miliary tuberculosis with meningitis .. .. .	+	4
19	" .. .. .	+	15
20	Generalized tuberculosis .. .. .	+++	14
21	Abdominal .. .. .	+++	4
22	Acute tuberculous broncho-pneumonia .. .. .	++	1½
23	Pulmonary tuberculosis with meningitis and intestinal ulcer	+	9
24	Miliary tuberculosis .. .. .	+	5
25	Tuberculous broncho-pneumonia—very acute type .. ..	++	3
26	" .. cervical lymphadenitis; acute miliary tuberculosis with meningitis .. .. .	+	7

**Control tests.**—In a hundred consecutive cases, sterile glycerine with 5 per cent. phenol was used as control, and in only one instance was there a reaction in the control arm. In this the tuberculin reaction was violently positive, was 30 mm. in diameter and was present for over six weeks, and the control reaction measured only 7 mm. across, and appearing in 12 hours, disappeared in 36 hours.

Taking the experience of other workers into account along with the above findings, it was not considered necessary to carry out control tests in further cases.

**The use of human and/or bovine tuberculin.**—In a hundred cases no instance was met with in which a bovine reaction was not accompanied by one to the human preparation while several cases reacted to the human and not the bovine tuberculin. These results were in keeping with those of other observers<sup>3</sup>, and in the rest of our series only the human tuberculin was used.

**The ease of performance.**—With a view to estimating the reliability of the method in the hands of those inexperienced in its use, the resident and other members of the hospital staff as well as two visiting post-graduates were invited to co-operate. After having been once instructed in the technique, each of these individuals independently and unassisted, carried out the test on 10 to 20 children who had been previously tested by us. Among 100 unselected children not one of the 34 reacting positively to our test failed to show a similar result when tested by another party.

In one instance a reaction was obtained by a house-physician in a case of convalescent pericarditis which had failed to react when tested by us two months previously, at a time when the patient was at the most critical stage of his illness. A repeat test following on the result obtained by the house-physician showed a positive reaction.

#### Discussion.

References to the original tattoo method are limited to those by Wahl and Austenberger<sup>1</sup> in 1923, and Forbes and Steinberg<sup>2</sup> in 1930. The first two mentioned, in their joint paper, found the method intermediate in reliability between the Pirquet and Mantoux test. Forbes and Steinberg on the other hand, while preferring the Mantoux to the Pirquet method, published a series of results embracing 398 cases in which the positive results for tattoo and Mantoux tests tallied with the exception of one instance in which no reading positive or negative was noted for the tattoo test. Our results as shown above suggest that the multiple puncture method loses nothing in reliability compared with either the Pirquet or Mantoux method.

Many investigators have reported failures of tuberculin tests in cases of massive tuberculosis<sup>5, 6</sup>, or in children wasted with long chronic disease<sup>6</sup>; failure is also said to occur where an acute illness associated with fever is present. On the other hand, McNeil<sup>8</sup> describes a modified method of performing the Pirquet test which in a limited number of cases he found not to fail even in massive tuberculous disease. As described above 350 children were subjected to the test using his technique and the results obtained in those cases which might be considered to be massive tuberculosis amply justified McNeil's claim. With regard to the multiple puncture method the results of our investigations suggest that it can lay claim to an equal reliability.

Using the multiple puncture test, no results were found to substantiate Smith's statement<sup>7</sup> that many children failing to react to a first test may do

so a few days later. We do, however, agree with this same writer that in using either the Mantoux test or any form of Pirquet test it is not always easy to discriminate between a true mild reaction and that due to trauma. This difficulty does not arise using the instrument described at the outset: with it trauma is reduced to a minimum, and in cases showing no reaction the test area is difficult to locate.

Wahl and Gustenberger consider that, in comparison with the Burr or Pirquet method and the intracutaneous method, the tattoo technique requires greater skill, and that the need of accurately judging the depth of the needle prick militates against the chances of establishing a dependable test. In their application of the tattoo method these writers use a fine needle 5-10

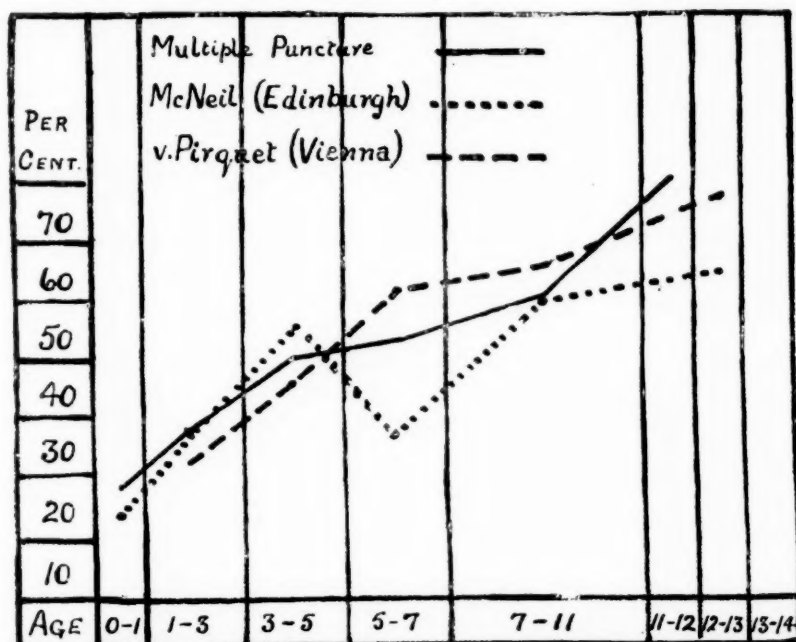


FIG. 3. Multiple puncture cutaneous tuberculin test. Percentage of positive reactions compared with results obtained by other cutaneous methods.

times in pricking through the tuberculin film, but by the use of the instrument described above, with its ease of control, it takes but little skill or practice to perform the test. Further, while experience allows of greater speed, even in the hands of the inexperienced, a considerable saving of time is effected as compared with other tuberculin methods, and no loss in reliability is incurred.

In Fig. 3 the results obtained in the present series have been plotted graphically against curves representing the findings of McNeil and Pirquet, and the close approximation of the graphs supports the contention that the tattoo method compares favourably with other methods. Our results (Table 3) show that the proposed technique is reliable in clinically manifest tuberculosis, and is also capable of revealing a latent infection (Fig. 4) where no clinical, bacteriological or radiological evidence has been demonstrated.

### Conclusions.

The multiple puncture method compares favourably with the Mantoux and Pirquet tests in all forms of tuberculosis in the matter of reliability.

It has distinct advantages over other methods in ease of procedure, speed of performance, absence of any but momentary slight discomfort, and absence of any tissue destruction even in the most violent reactions.

It is of particular value when used in children, especially for a routine method applicable to large numbers. The fact that it requires no particular skill in its performance makes the method especially suitable for use by anyone only occasionally carrying out a tuberculin test.

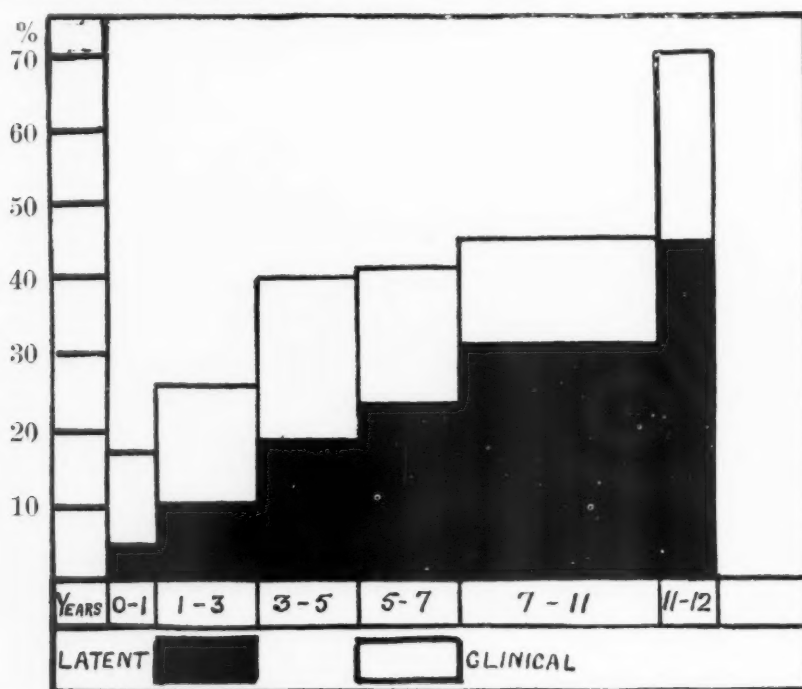


FIG. 4. Multiple puncture cutaneous tuberculin test: showing percentage of positive reactions at different age periods and relative incidence of latent and clinical cases.

My thanks are due to all physicians and surgeons of the Edinburgh Royal Hospital for Sick Children for granting access to their wards, and to other members of the hospital staff for their willing assistance.

### REFERENCES.

1. Craig, D. A., *J. Am. Med. Ass.*, Chicago, 1916, LXVII, 1227.
2. Forbes, R. P. & Steinberg, C. L., *Am. J. Dis. Child.*, Chic., 1930, XL, 1230.
3. McNeil, C., *Edinburgh Med. J.*, Edin., 1912, N. S., VIII, 324, 456.
4. Wahl, S. A. & Gustenberger, H. J., *Arch. Ped.*, N.Y., 1923, XL, 143.
5. Dickey, L. B., *Am. J. Dis. Child.*, Chicago, 1929, XXXVIII, 1155.
6. Dixon, A. B., *Brit. Med. J.*, Lond., 1931, i, 3668.
7. Smith, C. H., *Am. J. Dis. Child.*, Chicago, 1929, XXXVIII, 1137.
8. McNeil, C., *Brit. Med. J.*, Lond., 1923, i, 673.

# STUDIES IN JUVENILE RHEUMATISM

BY

CHRISTOPHER J. McSWEENEY, M.D., D.P.H.,

Deputy Medical Officer of Health, Cardiff.

The purpose of this review is to summarize the results of four years' special study in juvenile rheumatism among Cardiff school children. It will be convenient to describe our experiences under three headings—(1) the rheumatism clinic, (2) the hospital, and (3) the after-care of rheumatic children.

## The rheumatism clinic.

The clinic was inaugurated in 1927 and originally met once a fortnight. As the work expanded, in order to deal promptly with new cases and to keep in touch with all rheumatic children, weekly sessions were held during 1929. Later still, further sessions were found to be necessary, and between 1st January and 30th June, 1931, 42 sessions were held, an average of 7 a month. There was a total of 693 attendances at the rheumatism clinic during this period of

TABLE 1.  
INCIDENCE OF RHEUMATIC HEART DISEASE.

Area	Estimated population, 1929	Total cases	Cases per 1,000 of population	Estimated present school population	School cases per 1,000 of present school population
Cardiff .. ..	224,200	206	0.91	35,367	5.82
Bath .. ..	69,240	15	0.21	7,500	1.28
Bristol .. ..	391,320	754	1.90	54,673	7.72
Gloucestershire ..	329,346	89	0.27	53,501	1.03
Somerset .. ..	406,560	158	0.39	42,804	2.17
Wiltshire (excluding Swindon) .. ..	246,930	73	0.30	33,160	} 1.5
Swindon .. ..	62,020	13	0.20	10,238	

six months, 178 being new cases. On 30th June, 1931, there were 601 children remaining on the rheumatism register, a rate of 16.9 per 1,000 of the school population, or rather more than  $1\frac{1}{2}$  per cent. Of these, 206 were found to be suffering from heart disease, giving a figure of almost 6 per 1,000 for rheumatic heart disease amongst the present Cardiff school population. It is interesting to compare this figure with the rates of incidence recently given by Savage<sup>1</sup> in the interim report on the Gloucestershire, Somerset and Wiltshire inquiry (Table 1).

Cases are referred to the rheumatism clinic from school inspections and clinics, by private practitioners, public health nurses, teachers and school attendance officers. At each attendance a child receives a complete medical examination, special attention being paid to the heart. Frequency of re-examination in individual cases depends, of course, on the activity of the rheumatic process, but an effort is made to see every rheumatic child at least once in six months. Apart from the discovery of the early signs of rheumatic heart disease with a view to providing suitable hospital treatment, the main function of the clinic is educational. Parents receive instruction on the importance of juvenile rheumatism in the production of heart disease and the special care and management required by rheumatic children. Leaflets setting out the more essential points in this connection are also distributed. In order to be able to devote sufficient time to each case the numbers attending each session are restricted to 18 (5 or 6 being new cases), as we have not found it possible to deal adequately with more than this number at any one session of

TABLE 2.  
TYPES OF ONSET.

Origin	Cases ascertained during 1927		Cases ascertained during 1928-31		Total	
	No.	%	No.	%	No.	%
Rheumatic pains .. ..	79	37.4	230	55.4	309	49.3
Chorea .. ..	43	20.3	124	29.8	167	26.6
Rheumatic fever .. ..	55	26.0	46	11.0	101	16.1
Other definite symptoms ..	11	5.2	0	0.0	11	1.7
Insidious .. ..	23	10.9	15	3.6	38	6.0
Total .. ..	211	—	415	—	626	—

approximately three hours' duration. In the case of children not confined to bed, admission to hospital is always arranged through the clinic. Children who are too ill to attend the clinic are occasionally referred by their medical attendants, and these are seen at home by arrangement with the doctor, and, if considered suitable for admission, are conveyed to hospital by one of the City Council's ambulances.

The type of onset, the season and age at which it developed, and the ultimate condition of the heart in 626 children referred to the clinic during the last four years are set out in Tables 2-5. The findings concerning some 200 children included in this number and previously reported on<sup>2</sup> are given separately in Tables 2 and 5 for comparative purposes.

**Types of onset.**—The decline during recent years in the proportion of cases commencing with rheumatic fever which has been commented on by Gray Hill<sup>3</sup> and the relative increase in the milder types of onset are shown in Table 2. The significance of this tendency will be referred to later. It is interesting to find that 49 per cent. of 626 first attacks of the disease in Cardiff school children took the form of subacute articular rheumatism, as compared with 48 per cent. of 1,700 first attacks in London children<sup>4</sup>.

**Seasonal incidence.**—It will be seen in Table 3 that the majority of cases (66·3 per cent.) were found to commence during the cold wet months of winter and spring. If the cases beginning with chorea are excluded this tendency is accentuated. When the seasonal onset of chorea alone is investigated it is found that there is a greater likelihood of this manifestation occurring at the end of a school term, particularly in adolescent girls.

TABLE 3.  
SEASON OF ONSET.

	No.	%
Spring .. .. .	125	22·7
Summer .. .. .	107	19·4
Autumn .. .. .	78	14·1
Winter .. .. .	240	43·6
Uncertain .. .. .	550	—
	76	—
Total .. .. .	626	—

**Age of onset.**—It will be noted in Table 4 that in the great majority of instances in school children (73·7 per cent.) juvenile rheumatism commences between the ages of 5 and 10 years. When these figures are plotted out, the resultant curve closely approximates to that obtained for 1,700 rheumatic children recently reported on<sup>1</sup> by the School Medical Officer to the London County Council. The disproportionately low figure for cases beginning at the age of 14 years is, of course, artificial, being due to the intervention of the school-leaving age.

TABLE 4.  
AGE OF ONSET.

Age in years	No. of cases
2 .. .. .	4
3 .. .. .	14
4 .. .. .	36
5 .. .. .	70
6 .. .. .	67
7 .. .. .	72
8 .. .. .	84
9 .. .. .	75
10 .. .. .	65
11 .. .. .	42
12 .. .. .	38
13 .. .. .	20
14 .. .. .	1
Uncertain .. .. .	588
	38
Total .. .. .	626

433 (73·7%)

**Incidence of heart disease.**—The first column in Table 5 shows the condition of the heart in 214 rheumatic children ascertained before any special provision was made in Cardiff for rheumatic children. The second column shows the present condition of the heart in 412 children who had been dealt with during the three years the rheumatism supervisory scheme has been in operation.

Although the working of the clinic during the last three years has led to a fuller ascertainment of the earlier and milder forms of the disease in which cardiac involvement is less commonly encountered, it is fair to conclude that the lessened incidence of permanent heart disease amongst rheumatic children ascertained subsequent to 1927 is, in some measure, due to the establishment of the scheme which ensures the regular medical supervision of all rheumatic children and provides a special hospital for the treatment of early cases of carditis.

TABLE 5.  
INCIDENCE OF HEART DISEASE.

	Cases ascertained during 1927		Cases ascertained during 1928-31		Total	
	No.	%	No.	%	No.	%
Normal .. .. .	41	19.1	196	47.5	237	37.8
Cardiac abnormalities not amounting to permanent disease .. ..	44	20.5	120	9.1	164	26.2
Mitral regurgitation ..	101	60.2	69	23.3	170	35.9
Mitral stenosis .. ..	23		22		45	
Aortic regurgitation ..	3		2		5	
Aortic stenosis .. ..	0		1		1	
Aortic and mitral regurgitation .. .. .	2		1		3	
Mitral regurgitation and pulmonary stenosis ..	0		1		1	
	214	—	412	—	626	—

**Social status.**—In order to assess the significance, if any, of general environmental conditions in the ætiology of juvenile rheumatism, an attempt was made to grade 600 rheumatic children from the social standpoint, the following arbitrary standards being used :—

Grade A. Children from well-to-do homes.

Grade B. Those whose parents have a struggle to make ends meet, but who were not suffering from the effects of privation.

Grade C. Those who are destitute, semidestitute, or in receipt of public or charitable assistance.

The numbers in each group are shown in Table 6.

That poverty or destitution is not a potent factor in the causation of juvenile rheumatism is suggested by the fact that almost 75 per cent. of the children examined did not come within this category.

**Damp.**—The significance from the ætiological standpoint of damp in houses was also further investigated. Amongst 600 rheumatic children the houses were stated to be free of dampness in 61·1 per cent. of cases. In a control group of non-rheumatic children investigated in 1927 the percentage of houses not damp was 62·2 per cent. Clearly this factor is of little moment in the causation of juvenile rheumatism.

**Family incidence.**—The incidence of juvenile rheumatism in other members of the same family was also recorded. The result was rather surprising. In 125 out of 279 separate family histories investigated, one or more parents of rheumatic children had themselves suffered during childhood from some form of acute rheumatism—a percentage of 44·7. In all, 138 parents were affected. In investigating this factor, histories of rheumatic pains contracted in adult life as the result of war service, strain, or exposure of any kind were disregarded. Further, 385 rheumatic children were found to have 122 brothers or sisters affected with juvenile rheumatism. It would seem, then, that family relationships play a bigger part in the causation of juvenile rheumatism than has hitherto been realized.

TABLE 6.  
SOCIAL GRADE.

Social grade	No.	%
A	113	18·8
B	336	56·0
C	151	25·1
Total ..	600	—

**Infectivity.**—It was not possible to arrive at any definite conclusion with regard to the infectivity of juvenile rheumatism. The theory of the infective origin of this disease is attractive and has much to recommend it. The marked seasonal prevalence, the predominance of cases during the latter half of the first decade of life, and the tendency for other cases to occur in a family where one child is already affected, are suggestive features in this connection; but in the light of the facts ascertained from a scrutiny of over 600 case histories it must be admitted that, if the disease is communicable, its infectivity is of a low grade when compared with the exanthemata. If juvenile rheumatism is an infectious disease it would appear to be akin epidemiologically to the virus infections of the central nervous system, such as poliomyelitis and encephalitis lethargica. During the last four years many striking instances of multiple cases of juvenile rheumatism occurring contemporaneously in the same house have come to light, but on the other hand multiple cases have failed to occur in hundreds of other cases living under similar home conditions. The only conclusion that seems warrantable on the present evidence is that, while case-to-case infection in juvenile rheumatism is possible, it is neither the usual nor even a common mode of origin. The possibility of carrier spread and of

TABLE 7.  
COLOUR OF HAIR AND EYES.

Hair	No.	%	Eyes	No.	%
Fair .. .. .	111	34·6	Blue .. .. .	145	45·1
Medium fair .. ..	107	33·3	Grey .. .. .	49	15·2
Red .. .. .	16	5·0	Hazel .. .. .	20	6·2
Medium dark .. ..	39	12·1	Brown .. .. .	107	33·3
Dark .. .. .	48	14·9			
Total .. .. .	321	—	Total .. .. .	321	—

infection by sub-clinical types cannot, however, be ignored, and may be worthy of investigation when the bacteriological relationships of the disease are more clearly defined.

**Influence of scarlatina.**—The influence of scarlet fever in predisposing to juvenile rheumatism has received careful attention. Amongst 626 rheumatic children, 95 were found to have suffered from scarlet fever, and of these only 8 developed it after the first rheumatic manifestation. In 37 cases (almost 6 per cent. of the total rheumatic children examined) the onset of juvenile rheumatism was directly post-scarlatinal. Of these 11 were found to have permanent valvular disease and most of these had occurred before special hospital provision was made locally for rheumatic children. Of the 26 post-scarlatinal cases ascertained between 1928—1931 only three developed permanent heart disease. Our experience has been that when rheumatism develops after an attack of scarlet fever it is less likely to be followed by grave cardiac sequelæ than when the disease develops independently.

**Colouring.**—The colour of hair and eyes was recorded in 321 rheumatic children, and the results show that about two-thirds of the children were of the fair type and had blue or grey eyes. The figures are given in Table 7.

TABLE 8.  
INCIDENCE OF DENTAL CARIES.

	Rheumatic group		Non-rheumatic group	
	No.	%	No.	%
Sound teeth .. .. .	135	48·5	122	40·6
1 carious .. .. .	40	14·3	36	12·0
2 „ .. .. .	48	17·2	45	15·0
3 „ .. .. .	28	10·0	37	12·3
4 „ .. .. .	13	4·7	31	10·3
5 „ .. .. .	5	1·8	7	2·3
Over 5 carious .. ..	9	3·2	22	7·3
Total .. .. .	278	—	300	—

No distinctive type of complexion or facies was recognized, apart from this definite preponderance of fair children with blue or grey eyes. Chorea seemed to be the rheumatic manifestation exhibited by many of the dark-haired children.

**Dental caries.**—The incidence of dental caries amongst 278 rheumatic children was also investigated, and the findings as compared with those in a group of non-rheumatic children are set out in Table 8.

It will be seen that the incidence of carious teeth was slightly higher in the non-rheumatic group. It appears that dental caries may safely be discounted as a factor of aetiological significance in juvenile rheumatism.

### **The hospital.**

That some special form of institutional provision for rheumatic children was required in Cardiff has for years been apparent from the records of the School Medical Service. A special survey of Cardiff rheumatic children carried out in 1927<sup>2</sup> showed that in spite of the facilities then existing in general hospitals and convalescent homes, 129 children were suffering from permanent heart disease, the consequence of untreated or insufficiently treated juvenile rheumatism. How unsatisfactory the domiciliary treatment of juvenile rheumatism can be even in the homes of the well-to-do, is well known by all who have to deal with this disease in clinics and out-patient departments. The immediate needs of a child suffering from any form of acute or subacute rheumatism may be summed up in a few words—physical and mental rest until the disease subsides. Even if rest in bed can be ensured in a working-class home, it is at best a make-shift. The mother, busy with household tasks and the care of the other children, is frequently unable to provide the amount of supervision and care required by the ailing rheumatic child. In the days before the City Council had provided special hospital accommodation for these cases, it was not unusual for children to continue attending the clinic with active rheumatism for nine and twelve months at a stretch, and in these circumstances it will be realized that eventual cardiac involvement was the rule. Since the Lord Pontypridd Hospital was opened on 8th April, 1929, conditions have completely changed, for it is found that the most intractable of rheumatic manifestations speedily respond to a comparatively short period of in-patient treatment. Our aim in selecting cases for hospital has been to admit only those who are in a sufficiently early stage of heart disease to respond to treatment. Any rheumatic child presenting the signs of early carditis as below described is considered a suitable case for admission. In addition, all acute forms of juvenile rheumatism (rheumatic fever, chorea, and severe rheumatic pains), even though the heart may appear normal on clinical examination, are regarded as potential cases of heart disease and so qualify for hospital treatment. In subacute cases a period of observation at the clinic is sometimes necessary before the question of hospital treatment can be decided. It occasionally happens that a child has a permanent valvular condition present on admission to hospital. These are usually cases suffering from acute manifestations (e.g., chorea, arthritis or severe pains) and the determining factor in their

admission has often been the knowledge that the patient cannot secure in the unsatisfactory environment of his own home the rest and care required to carry him safely through an acute attack. Again, a child found to have early carditis when seen at the clinic may develop the signs of valvular disease while awaiting admission to hospital. This is more prone to happen in the winter and spring when the demand on the hospital accommodation is heaviest. Starting with 16 beds, the accommodation has been increased to 25, but the experience gained during two winters indicates that even this is insufficient for our present needs. In a city like Cardiff it is probable that one bed for every 1,000 of school population (approximately 35 beds) would not be an excessive provision for this type of case.

In the period April 8th, 1929, to July 31st, 1931, there were 249 admissions to hospital. Of these, 10 children were transferred to other Corporation hospitals (9 cases of communicable disease and one case of the post-encephalitic syndrome which had been admitted in error as chorea). 17 children were for various reasons withdrawn by their parents after short periods, leaving 222 cases treated to a conclusion in the wards for one or other form of juvenile rheumatism. All children admitted were of school age. The form of rheumatism present on admission to hospital in these cases was as follows :

Chorea .. .. .	118 cases
Rheumatic pains .. .. .	111 ..
Rheumatic fever .. .. .	8 ..
Early carditis without definite symptoms .. .. .	12 ..
<hr/>	
Total .. .. .	249 cases

One child died in hospital after almost five months' hospital treatment. She was a girl aged 11 who was admitted with severe chorea of three months' standing and an active carditis causing mitral regurgitation. She remained completely uninfluenced by all treatment while in hospital and had two attacks of cerebral embolism, the second causing a left-sided hemiplegia. The clinical course of this case corresponded closely to the variety of sub-infective endocarditis described by Horder and others under the title of endocarditis lenta. One other advanced case of mitral stenosis and acute chorea, admitted after tonsillectomy at the urgent request of the parents, developed rapid failure of compensation and died three days after transfer to a general hospital. The remaining 220 cases were discharged free of active disease.

In the great majority of cases some abnormality of the heart was detectable on admission to hospital. In more than half of the cases this took the form of early carditis, but reference to Table 9 shows that no less than 47 of the 222 cases treated to a conclusion were thought to be suffering from permanent valvular disease on admission. Although cases with established heart disease are not, generally speaking, considered suitable for this type of institution, their admission has in several instances unexpectedly justified itself, for with prolonged rest and treatment definite murmurs have disappeared and the heart has returned to normal functional capacity. Even with increasing experience it is not always possible to decide, on clinical examination, whether

certain lesions of the heart, of comparatively recent origin, are likely to respond to treatment or not. In these cases the practice is to give the child the benefit of the doubt, and accordingly seven children, classified on admission as having established valvular conditions, completely lost all signs of heart disease after a prolonged period of in-patient treatment, while four others were regarded on discharge as not suffering from valvular disease, although the heart sounds had not quite regained their normal clearness.

**Cardiac complications.**—The most constant physical sign of early rheumatic carditis in our experience has been enlargement of the area of cardiac dullness, coupled with an alteration in the character of the first sound of the heart. The alteration in the great majority of cases takes the forms of blurring or a want of clearness, and this is usually accompanied by an accentuation of the second sound. Sometimes the first sound is definitely roughened and prolonged, or again, the muscular element in it may be lacking, rendering it valvular in character. In extreme cases the first sound may be entirely inaudible, and at a later stage in the disease a soft systolic murmur localized to the mitral area makes its appearance. It is probable that all these signs express myocardial rather than endocardial mischief, and with the exception of the absence of the first sound and the localized murmur it is the rule for these abnormalities to disappear with prolonged rest in bed. If the condition is ignored, however, the development of permanent valvular disease is almost invariable. In the case of localized murmurs or absence of the first sound, complete recovery is not impossible, but a more usual result is some degree of hypertrophy of the cardiac musculature with a slighter degree of impurity in the character of the sounds. When endocardial damage sufficient to evoke the classical signs of disease exists, it is, of course, the exception for the heart to return to normal or for any improvement other than increased hypertrophy of the left ventricle to take place, but the existence of a systolic murmur at the mitral area which is conducted around to the interscapular region is not conclusive proof that the valvular defect is permanent. A very few of these cases do respond to treatment, and if it is known with certainty that such a conducted murmur is of recent origin it is always worth while trying the effect of rest in hospital before deciding that the physical signs connote irretrievable damage to the valve tissues. A change in the quality of the sounds of the heart, or in the adventitious sounds accompanying or replacing them, does not readily occur when the condition is one of long standing and the disease is quiescent, but the clearness of the sounds and the character of the bruits expressing early carditis do change within relatively short periods. With these changes detectable on auscultation there will be present the other invariable sign of active carditis, namely, an alteration in the size of the area of cardiac dullness. Another constant sign of active carditis is a change in the rate of the pulse. In assessing the activity of rheumatic disease of the heart, pulse, rather than temperature readings, should receive primary consideration. In addition to the usual twice daily record, which should preferably be graphed, it is desirable, in the case of children, to chart the rate of the sleeping pulse, and if a heart, not the seat of an established valvular condition, gives readings persistently

over 90 during sleep, the case should be very closely watched for other signs of rheumatic carditis. Persistent frequency of the pulse may be the earliest sign of active carditis. It is often the only sign for perhaps several weeks on end. A fluctuating pulse, especially with evening readings reaching 100, is another suspicious circumstance, but in emotional children and in the absence of a frequent sleeping pulse, too much importance should not be attached to this. Irregularity in rhythm may or may not connote active carditis. It is much more frequently found in established valvular disease. It is a safe rule to insist on absolute recumbency, even during meals, wherever the sleeping pulse of a rheumatic child who has not an established valvular leak exceeds 90 on three consecutive evenings. It cannot be too strongly emphasized that hearts can become progressively damaged from rheumatism without any appreciable pyrexia, and, indeed, without any obvious constitutional disturbance. Thus a scrutiny of the charts of 216 consecutive cases showed that the pulse readings alone were elevated in 92, the temperature alone in 24, and both in 37.

One of the most unexpected of our experiences has been the comparative rareness of long continued pyrexia in the acute and sub-acute cases of the disease treated in the wards. It is, of course, common for the temperature to be elevated when a joint is swollen, but defervescence is generally very speedy, a matter of a few days at most. No doubt the complete immobilization of patients which the hospital régime prescribes helps to produce this effect, but it is difficult to avoid the conclusion that juvenile rheumatism is to-day a much less acute disease than it was formerly. It should, however, be pointed out that this milder symptomatology of present-day rheumatism is not in any way analogous with the mildness of modern scarlet fever and smallpox, for cardiac involvement is an integral part of juvenile rheumatism and there is no evidence that the prevalent insidious forms of the disease are less likely to lead to heart mischief. Indeed, the converse may be true, for with the less severe manifestations now encountered there is less disposition on the part of parents to seek medical advice at a sufficiently early stage of the disease to render preventive treatment practicable.

The aim in treatment is to safeguard the heart during the acute and sub-acute phases of the disease, and, so far as is possible, by the provision of rest and careful management, to prevent the development of permanent cardiac damage. Broadly speaking, this object is attained by the insistence on absolute rest in bed during the acuter stages, followed by a very gradual return to normal activities when the disease has become quiescent. It is essential to keep the child completely at rest during the active phases of rheumatism. During the first fortnight after admission to hospital the child is closely observed and questioned for signs and symptoms. He is kept lying flat in bed and is allowed to do nothing for himself, and is fed by a nurse. To ensure freedom from emotional upsets visits from relatives are not allowed during the first week, at the end of which time the child has usually grown accustomed to the ritual and the personnel of the hospital. At the end of the fortnight the extent and degree of activity will have been gauged. As long as there are any signs of

active disease the patient is kept lying flat and usually for the whole of this time he is not allowed to feed himself. The subsequent management of the cases depends largely on the development of signs and symptoms. In a case speedily responding to rest the patient may be allowed to sit up in bed for 20 minutes each day a week or so after the commencement of self-feeding. The effect of each concession on the pulse rate, the quality of the heart sounds and the area of cardiac dullness is carefully noted, and if no ill effects follow, increments of 20 minutes are added to the sitting-up period every two or three days until the patient is sitting up for three hours each day. About a week later he is allowed to get up and sit about the ward, and subsequently proceeds to walk about the grounds, first on the flat and later without restrictions. This is an account of the straightforward case pursuing an uneventful course towards recovery, but this régime is liable to interruptions. Elevation or fluctuations in the pulse or temperature readings, alteration in the character of the heart sounds or in the area of cardiac dullness, return of twitchings or pains, increase in pallor, the development of nose bleeding, or the appearance of purpuric patches or urticarial rashes, e.g., erythema marginatum, may determine a withholding of further concessions or a return to complete recumbency. Persistent frequency or fluctuations of the pulse rate is always taken as an indication for complete immobilization in bed. Sometimes in spite of this treatment the heart condition steadily progresses until a systolic murmur makes its appearance. It is surprising how satisfactory may be the general condition of the child while this change is taking place. There may be a complete absence of pains or movements, but usually the colour is poor and there is, in addition, the instability of the pulse rate and possibly of the temperature. If a murmur does evolve, it is, at first, audible only at the mitral area, but in the course of a few weeks it becomes more distinct locally and is now heard in the axilla and still later in the inter-scapular area. Enlargement in the area of cardiac dullness accompanies the development of these physical signs, but the process of progressive cardiac involvement may stop at any intermediate stage, leaving most commonly a murmur localized to the mitral area which persists after the disease has become quiescent. Sometimes this local bruit, after remaining stationary for many weeks, may clear up and the heart may be again free of murmurs. More usually in this type of case some softening of the first sound is left together with a degree of cardiac enlargement. In the earlier phases of rheumatic carditis signs of pericardial involvement have been constantly looked for, but so far have not been encountered. Pre-cordial pains are, however, not uncommon in this stage and may express a slight degree of pericardial inflammation. As shown by Table 9, the mitral valve has, in the great majority of cases, been the seat of endocardial involvement.

In the treatment of these rheumatic conditions little use is made of drugs. Salicylates are used for the relief of pain chiefly. Aspirin has been tried with the hope of cutting short relapses, but no striking results have yet been obtained. Precipitated calcium in lactic acid has been given to the severer cases of chorea with a preparation containing the Vitamins A and D, but the cases so treated

did not appear to lose their movements any more rapidly than those who were treated merely by rest. Iron tonics are used regularly for combating the anæmia associated with the disease, and various proprietary preparations containing cod-liver oil are given to children with subnormal nutrition. No modification in the diet of these children is considered necessary. An ample and nourishing diet is given in all cases, solids being withheld only when the temperature exceeds 100° F.

The value of open-air in the treatment of juvenile rheumatism has been amply demonstrated since the inception of this work. During the summer months as many as possible of the beds are wheeled out on the lawn, and on fine days the children lie exposed to the sunlight wearing a minimum of clothing. For the whole of the summer two shelters in the grounds are utilized

TABLE 9.

EFFECT OF HOSPITAL TREATMENT ON CONDITION OF HEART.

Condition of the heart					On admission		On discharge	
					No.	%	No.	%
Myocardial conditions	..	..	..	..	116	52.2	30	13.5
Blurred first sound	..	..	..	..	100		29	
Valvular first sound	..	..	..	..	14		0	
Absent first sound	..	..	..	..	2		1	
Endocardial conditions	..	..	..	..	77	34.6	57	25.6
Localized murmur	..	..	..	..	30		19	
Mitral regurgitation	..	..	..	..	35		22	
Aortic regurgitation	..	..	..	..	0		1	
Mitral and aortic regurgitation	..	..	..	..	1		1	
Mitral stenosis	..	..	..	..	10		13	
Mitral regurgitation and pulmonary stenosis	..	..	..	..	1		1	
Normal hearts	..	..	..	..	29	13.0	135	60.8
Total	..	..	..	..	222	—	222	—

as open-air wards and accommodate six children with a nurse who sleeps there at night. The children in the shelters improved much more rapidly in general health, became deeply pigmented and seemed to lose their rheumatic manifestations more quickly than those sleeping indoors. It was observed that the children who had been treated in the open-air shelters seemed less liable to relapses after discharge and the pigmentation of the skin acquired by these children persisted for many months after they had left hospital. It is to be regretted that the construction of the hospital (which is an adapted private residence) does not permit of the application of open-air treatment on a much wider scale.

The results obtained from hospital treatment so far as the heart was concerned in the first 222 cases are set out in Table 9.

It will be observed that 116 definitely myocardial conditions on admission were reduced to 30, that 77 cases regarded as endocardial on admission were reduced to 57 on discharge, and that the figure for normal hearts (29) on admission was raised to 135 on discharge. Up to the present the great majority of the cases treated in hospital are remaining well. In dealing with a disease like rheumatism relapses must be expected, and it is this tendency which makes the periodical medical examination of rheumatic children so essential a feature of any scheme attempting to deal with the problem. So far the indications are that the children discharged from hospital continue to keep well, recurrences being milder in character and more fleeting in duration than in the case of children who have not undergone in-patient treatment. The educational value of the hospital treatment undoubtedly plays a large part in producing this effect, as it has been noted again and again that even quite young children absorb sufficient of the spirit of the hospital régime to render subsequent domiciliary treatment a very much simpler matter from the parents' point of view.

**Complications other than cardiac.**—Having regard to the speedy subsidence of acute symptoms which complete immobilization effects, it is not surprising that complications other than cardiac arising during hospital treatment should be very few. Amongst 222 cases of acute and sub-acute rheumatism, whose combined treatment in hospital exceeded 15,000 days, the following complications were observed :—

Pharyngitis and tonsillitis	..	..	..	..	..	24
Periodontal abscess	..	..	..	..	..	2
Otitis and otorrhœa	..	..	..	..	..	4
Urticaria	..	..	..	..	..	5
Purpura	..	..	..	..	..	4
Herpes zoster	..	..	..	..	..	3
Rhinitis	..	..	..	..	..	3
Conjunctivitis	..	..	..	..	..	3
Epistaxis	..	..	..	..	..	6
Bronchitis	..	..	..	..	..	1

The occurrence of throat inflammations and their effect on the rheumatic process has been closely watched. During treatment 19 children developed a total of 24 attacks of either tonsillitis or pharyngitis. In 10 instances the attack of tonsillitis or pharyngitis preceded a relapse by periods varying from one to four weeks. In the remaining cases the throat inflammation seemed to produce no effect. It was noticed that in 12 other cases who did not complain of sore throat, but who had sudden rises in temperature lasting for 24 hours, relapses followed within a similar period, generally two or three weeks after the elevation in temperature. The relapses in all cases involved the heart and were never choreic in nature. The significance of these sharp attacks followed by an intermediate period of quiescence and then a relapse may be, as suggested by the writings of Schlesinger<sup>5</sup>, Sheldon<sup>6</sup> and Collis<sup>7</sup>, the presence in the throat during the period of initial fever of the hæmolytic streptococcus which leads to an allergic response in tissues sensitized by previous infection. No bacteriological investigations have been so far carried out in Cardiff in this connection.

It was observed amongst the children in hospital that the tendency towards an attack of tonsillitis seemed to be quite independent of the state or size of the tonsils, and in three-fourths of the children developing attacks while under treatment the tonsils were either normal or had been completely removed by previous tonsillectomy. The results obtained in 1927, when a group of rheumatic children was compared as to the state of their tonsils with a control group of non-rheumatic children, have been confirmed by subsequent observation (see Table 10).

TABLE 10.  
STATE OF TONSILS.

Tonsils	Rheumatic children		1927 controls	
	No.	%	No.	%
Normal .. .. .	276	46.9	54	46.3
Slightly enlarged .. .. .	131	22.2	31	26.7
Moderately enlarged .. .. .	68	11.5	13	11.2
Enlarged .. .. .	45	7.6	10	8.6
Removed .. .. .	68	11.5	8	6.9
Total .. .. .	588	—	116	—

Allowing for the disproportion in the size of the two groups, it is obvious that there is no definite relationship between the state of the tonsils and the development of juvenile rheumatism.

Mere frequency of sore throats seems also to possess no aetiological significance (see Table 11).

TABLE 11.  
INCIDENCE OF SORE THROATS.

Sore throat	Rheumatic children		Non-rheumatic controls (1927)	
	No.	%	No.	%
Never .. .. .	407	65.8	82	70.6
Very rare .. .. .	37	5.9	6	5.0
Occasional .. .. .	98	15.8	15	12.8
Frequent .. .. .	76	12.2	13	11.2
Total .. .. .	618	—	116	—

It is possible that the importance of throat conditions in this disease may be found to depend more upon the bacteriological findings during pyrexial periods than upon alterations in the size, or frequency of inflammation, of the tonsils.

The experience of the last three years has also confirmed the view expressed in 1928<sup>2</sup> that tonsillectomy does not prevent the onset of juvenile rheumatism, for of 407 rheumatic children examined since then, 51 had had their tonsils

removed and of these no less than 39 (76 per cent.) were operated upon before the first sign of rheumatism manifested itself. Having regard to the frequency with which an acute attack of chorea is precipitated by tonsillectomy and the questionable influence of the operation in the prevention of other forms of rheumatism, it is clear that the indiscriminate removal of tonsils in rheumatic children should be condemned. Striking instances of how an injudicious tonsillectomy can light up a quiescent cardiac condition with dire results have been given by Coburn<sup>8</sup> in his treatise on the rheumatic state recently published.

#### **The after-care of rheumatic children.**

Children discharged from hospital rest quietly at home for one month and are then re-examined at the clinic. In the majority of cases they are then found fit to return to school, but in some cases a further period of rest at home is necessary before return to school. With some children it may be necessary even to resume school more gradually, the child attending the afternoon session only, and resting in bed in the mornings. As a general rule children who have had acute attacks do not return to school for at least three months after the onset, and, on an average, two months of this period is spent in hospital. There are, of course, instances which require much longer periods of rest than this, and a few children with insidious forms of carditis have been in hospital for periods of six or eight months at a time. Owing to the pressure on the accommodation at the hospital, cases have undoubtedly to be sent home too soon after getting up and, although in the majority of cases the mothers can be trusted to supervise the completion of convalescence, there have been instances where children have relapsed after longer or shorter intervals of home management. Out of the total admissions up to July 31, 1931, 18 were re-admissions, 16 children undergoing two periods of hospital treatment and one child three. The latter had two attacks of severe chorea and one of rheumatic fever in eighteen months, but was finally discharged with a normal heart. In most of the cases re-admitted the home conditions had been unfavourable and the parental management unsatisfactory.

Generally speaking, the cases which have passed through the hospital have remained well and any recurrences occurring have been slight and of brief duration. Co-operation with the school attendance department has now been developed to such an extent that rheumatic children not excluded from school are readily excused from attending on particularly wet days, especially if they would be obliged to walk a long distance in order to do so. The willing co-operation of head teachers and school attendance officers in making special arrangements in respect of the attendance of rheumatic school children is deserving of mention.

An experiment was begun at Easter, 1930, of sending to an open-air school a certain number of rheumatic children, who, although free of rheumatic manifestations when discharged from hospital, were still of subnormal physique. The children selected were those who had escaped the graver cardiac sequelæ and were of the type who seemed likely to benefit from the open-air conditions

and the regular and balanced diet available at the open-air school. It need hardly be mentioned that the unmodified school régime cannot be followed by the rheumatic child, but with adequate precautions as to exposure to the weather and restriction of exercise and recreation it is clear that selected rheumatic children can make considerable progress at an open-air school. The factor of continuous medical supervision which is available at this type of school has special advantages in the case of the rheumatic child, for recurrences can be detected at an early stage and appropriate advice and treatment prescribed.

While there can be no question as to the value of special hospital treatment in bringing about a speedy subsidence of the acute or sub-acute manifestations of juvenile rheumatism, it is, of course, far too early yet to express any opinion as to its effect in lessening the incidence of heart disease amongst the general population. All that can be said at present is that the hospital treatment of the earlier phases of rheumatic carditis, coupled with the regular medical supervision of rheumatic children, gives results which are encouraging enough to hold out the hope that a disease which has been estimated by some to be responsible for 25,000 deaths every year in England and Wales may yet prove to be largely, if not entirely, preventible.

#### Summary.

(1) A four years' survey of juvenile rheumatism in Cardiff showed that 16.9 per 1,000 of the school population are affected, of whom 5.82 were suffering from rheumatic heart disease.

(2) Further evidence of the relative decrease in the prevalence of rheumatic fever at the expense of the milder and more insidious forms of juvenile rheumatism was obtained.

(3) Among 550 case histories investigated, the onset of the disease occurred during the winter or spring months in 475 (86.3 per cent.).

(4) Among 588 rheumatic children 433 (73.7 per cent.) developed the first rheumatic manifestation between the age of 5 and 10 years.

(5) Among 626 rheumatic children examined 225 (35.9 per cent.) were found to be suffering from permanent disease of the heart.

(6) An investigation of the social conditions under which 600 rheumatic children lived showed that almost 75 per cent. of the children were not suffering from the effects of poverty or privation.

(7) Further support for the view that dampness of houses is a factor of no ætiological significance in juvenile rheumatism was obtained.

(8) The parents of rheumatic children were found to have themselves suffered from juvenile rheumatism in 44.7 per cent. of 279 separate family histories investigated, and 385 rheumatic children were found to have 122 brothers or sisters affected with the disease.

(9) Although family relationships play some part in the causation of the disease no conclusive evidence as to the infectivity of juvenile rheumatism came to light.

(10) In 6 per cent. of 626 cases the onset of the disease was directly post-scarlatinal but the post-scarlatinal cases were found to be less likely to develop cardiac sequelæ than those developing the disease independent of scarlet fever.

(11) No distinctive type of rheumatic child was recognized, but a majority of the children were fair-haired and had either blue or grey eyes.

(12) The incidence of dental caries was found to be no higher in rheumatic than in non-rheumatic children.

(13) A clinical description of the earlier phases of rheumatic carditis is given, and the methods and results of hospital treatment in 222 cases outlined.

(14) The significance of throat conditions in juvenile rheumatism is discussed. Figures are given to support the contention that the state of the tonsils is of little importance in the causation of this disease.

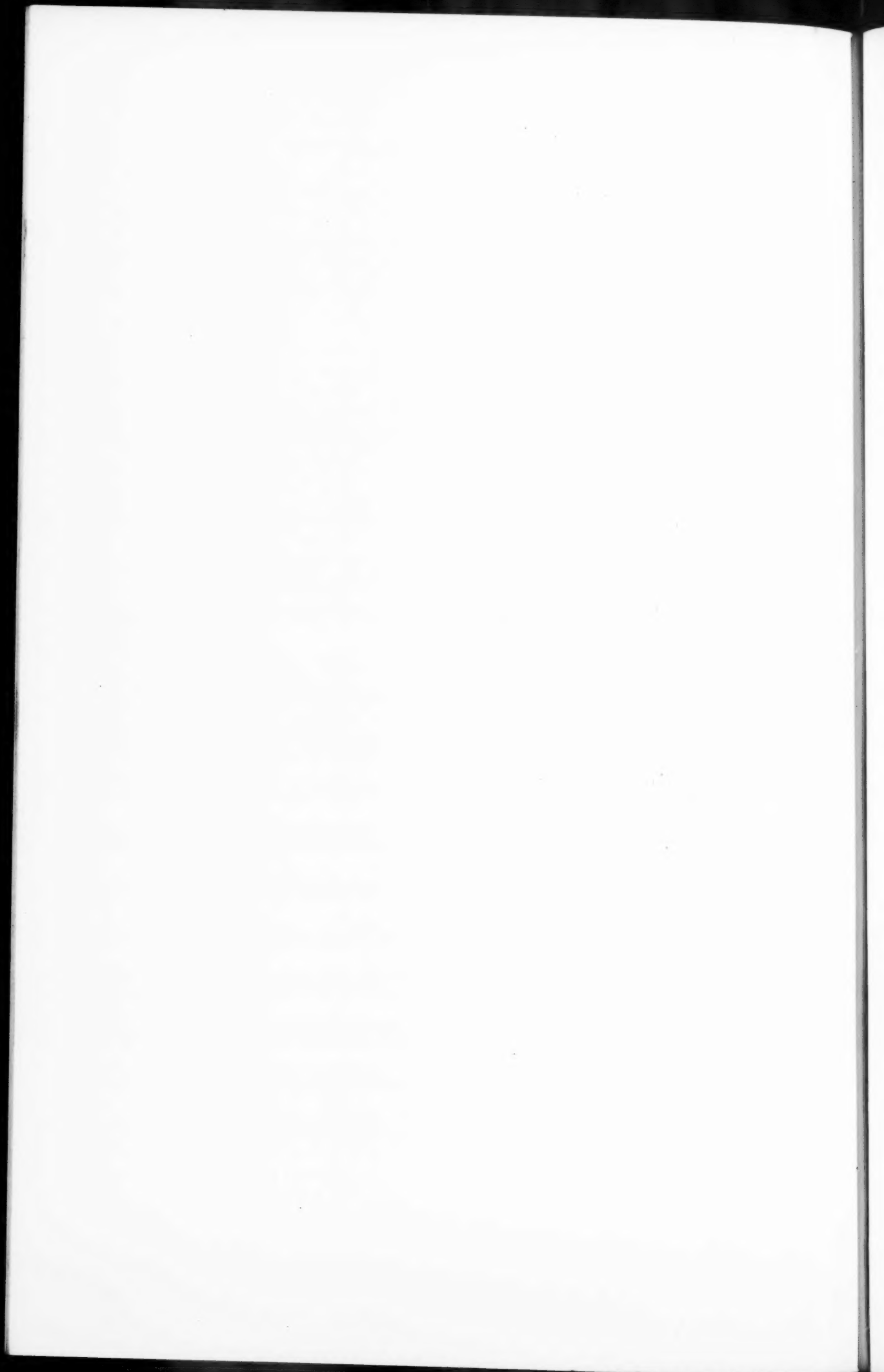
(15) Further evidence is adduced as to the limitations of tonsillectomy in the treatment of juvenile rheumatism.

(16) The effect of open-air treatment in the hospital treatment and after-care of rheumatic children is described.

I wish to express my thanks to Dr. Ralph M. F. Picken, Medical Officer of Health, Cardiff, for his kind permission to publish these notes.

#### REFERENCES.

1. Savage, W. G., *Brit. Med. J.*, London, 1931, ii, Supp., 38.
2. McSweeney, C. J., *Lancet*, London, 1928, i, 959.
3. Gray Hill, N., *Brit. J. Child. Dis.*, London, 1930, XXVII, 161.
4. Kay Menzies, F. N., *Ann. Rep., School Med. Off., L.C.C.*, London, 1931.
5. Schlesinger B., *Arch. Dis. Child.*, London, 1930, V, 411.
6. Sheldon, W., *Lancet*, London, 1931, i, 1,337.
7. Collis, W. R. F., *Loc. cit.*, 1,341.
8. Coburn, A. F., *The Factor of Infection in the Rheumatic State*, London, 1931, 251 *et seq.*



# INDEX TO VOLUME VI.

- Alkali in salicylate therapy, the value of (Noah Morris and Stanley Graham), 273.
- Alkalosis in the vomiting of infancy (Montague Maizels), 293.
- ALLEN, F. M. B. (and H. I. McClure): Study of intracranial hemorrhage in the new-born infant, 97.
- Anæmia, splenic, familial (S. L. Ludbrook), 239.
- Blindness, night, and nutritional xerophthalmia (J. C. Spence), 17.
- Blood cholesterol in childhood (Kathleen M. Ward), 329.
- Blood, phosphorus compounds and calcium in (Milan Sokolovitch), 183.
- Bone, cystic disease of (Norman Capon), 258.
- BRAY, GEORGE W.: Enuresis of allergic origin, 251, 257.
- British Paediatric Association, *see* Paediatric.
- Bronchiectasis, prognosis in (Leonard Findlay and Stanley Graham), 1.
- BROWNE, DENIS: The surgical anatomy of Rammstedt's operation, 129.
- Calcium and the phosphorus compounds in the blood of children, distribution of (Milan Sokolovitch), 183.
- Calcium and phosphorus metabolism in nephritis (Findlay J. Ford), 209.
- CAPON, NORMAN: Cystic disease of bone in an infant, 258.
- Chloride metabolism in congenital pyloric stenosis (Noah Morris and Stanley Graham), 27.
- Cholesterol, blood, in children (Kathleen M. Ward), 329.
- Celiac disease, metabolic studies in (Olive Macrae and Noah Morris), 75—(A. P. Thomson), 258.
- Convulsions in infants (D. W. Winnicott), 257.
- CRAIG, JOHN (and Alexander Mitchell): Spinal tumours in childhood, 11—Malignant hypertension in childhood, 157, 256.
- CRAIG, W. S.: The multiple puncture cutaneous tuberculin test, 357.
- Cystic disease of bone in an infant (Norman Capon), 258.
- Death, sudden, in infancy and childhood (J. M. Smellie), 257.
- DEEM, HELEN EASTERFIELD: The milk of New Zealand women, 53.
- Diabetes, infantile, with gangrene (R. D. Lawrence and R. A. McCance), 343.
- Diet, ketogenic, some effects of (R. W. B. Ellis), 258, 285.
- DODDS, GLADYS H.: Otitis media with purulent meningitis in an infant 9 days old, 71.
- DOOLEY, PARKER: The incidence of undulant fever in children, 235.
- Duodenal obstruction in the new-born, three cases of (C. P. Lapage, Annie E. Somerford, and Fanny Howe), 307.
- Duodenal ulcer, *see* Ulcer.
- Ectopia cordis (K. D. Wilkinson), 257.
- Electrocardiogram of normal school children (C. Bruce Perry), 259.
- ELLIS, R. W. B.: Some effects of a ketogenic diet, 258, 285—(and W. G. Wyllie): The clinical interpretation of some hæmorrhagic states, 313.
- ELLISON, J. B.: Pneumonia in measles, 37.
- Enuresis of allergic origin (George W. Bray), 251, 257.
- Fever, undulant, in children (Parker Docley), 235.
- FINDLAY, LEONARD (and Stanley Graham): Prognosis in bronchiectasis, 1—The incidence of the rheumatic infection, 256.
- FORD, FINDLAY J.: Calcium and phosphorus metabolism in nephritis, 209.
- GAISFORD, WILFRID: Case of congenital hypertrophic pyloric stenosis, 111.
- Gangrene in an infant associated with temporary diabetes (R. D. Lawrence and R. A. McCance), 343.
- GIBBENS, J. HARTLEY: The primary infection of tuberculosis, 258.
- GRAHAM, STANLEY (and Leonard Findlay): Prognosis in bronchiectasis, 1—(and Noah Morris): The chloride metabolism in congenital pyloric stenosis, 27—The value of alkali in salicylate administration, 256—(and Noah Morris): The value of alkali in salicylate therapy, 273.
- GREGORY, HAZEL H. CHODAK: Two cases of sub-acute hepatic necrosis, 101.
- Growing pains, race, rheumatism and (J. C. Hawksley), 303.
- Hæmorrhage, intracranial, in the new-born infant (F. M. B. Allen and H. I. McClure), 97.
- Hæmorrhagic states, clinical interpretations of some (W. G. Wyllie and R. W. B. Ellis), 313.
- HAMPSON, A. C.: Tumours of the parathyroid glands, 257.
- HARRISON, L. PRISCILLA: A case of perforated duodenal ulcer in an infant, 245.
- HAWKSLEY, J. C.: Race, rheumatism and growing pains, 303.
- Heart, congenital anomalies of in elementary school children, 265.
- Hepatic necrosis, sub-acute (Hazel H. Chodak Gregory), 101.
- HOWE, FANNY (C. P. Lapage and Annie E. Somerford): Three cases of duodenal obstruction in the new-born, 307.
- HUTCHISON, ROBERT: Neoplasm of suprarenal cortex in an infant of 4½ months, 257.
- Hydrocephalus, treatment of (Eric Pritchard), 258.
- Hypertension, malignant, in childhood (John Craig), 157, 256.
- Jaundice in infancy (R. C. Jewesbury), 256.
- JEWESBURY, R. C.: Two cases of jaundice in infancy, 256.
- Ketogenic diet, *see* Diet.
- LANGMEAD, F.: Role of hæmolytic streptococci in the causation of arthritic purpura, 255.
- LAPAGE, C. P. (Annie E. Somerford and Fanny Howe): Three cases of duodenal obstruction in the new-born, 307.
- LAWRENCE, R. D. (and R. A. McCance): Gangrene in an infant associated with temporary diabetes, 343.
- LIGHTWOOD, R. C.: Neoplasm of suprarenal cortex in an infant of 4½ months, 257.
- LLOYD, ERIC I. (and Wilfrid Sheldon): Two cases of double ureter, 231.
- LUDBROOK, S. L.: Familial splenic anæmia, 239.
- MCCANCE, R. A. (and R. D. Lawrence): Gangrene in an infant associated with temporary diabetes, 343.
- MCCLURE, H. I. (and F. M. B. Allen): Study of intracranial hæmorrhage in the new-born infant, 97.

- MACRAE, OLIVE (and Noah Morris): Metabolism studies in coeliac disease, 75.
- MC SWEENEY, CHRISTOPHER J.: Studies in juvenile rheumatism, 367.
- MAIZELS, MONTAGUE: Alkalosis in the vomiting of infancy, 293.
- Malignant hypertension, *see* Hypertension.
- Measles, pneumonia in (J. B. Ellison), 37.
- Meningitis, purulent, with otitis media in an infant (Gladys H. Dodds), 71.
- Metabolism, chloride, in congenital pyloric stenosis (Noah Morris and Stanley Graham), 27.
- Metabolism studies in coeliac disease (Olive Macrae and Noah Morris), 75.
- Milk of New Zealand women (Helen Easterfield Deem), 53.
- MITCHELL, ALEXANDER (and John Craig): Spinal tumours in childhood, 11.
- MORRIS, NOAH (and Stanley Graham): The chloride metabolism in congenital pyloric stenosis, 27—(and Olive Macrae): Metabolism studies in coeliac disease, 75—(and Stanley Graham): The value of alkali in salicylate therapy, 273.
- NABARRO, DAVID: Congenital syphilis, 258.
- NEALE, A. VICTOR: Acute and chronic non-tuberculous pyuria in children, 165.
- Necrosis, sub-acute hepatic (Hazel H. Chodak Gregory), 101.
- Neoplasm of suprarenal cortex (Robert Hutchison and R. G. Lightwood), 257.
- Nephritis, calcium and phosphorus metabolism in (Findlay J. Ford), 209.
- New Zealand women, the milk of (Helen Easterfield Deem), 53.
- Night-blindness and nutritional xerophthalmia (J. C. Spence), 17.
- Otitis media with purulent meningitis in an infant (Gladys H. Dodds), 71.
- PEDIATRIC ASSOCIATION, BRITISH:—  
Annual meeting, 255;  
Election of officers, 255;  
Next meeting, 255;  
Treasurer's report, 255;  
Change of rules, 255;  
'Save the Children' Union, 255;  
Scientific communications, 255;  
Role of hæmolytic streptococci in the causation of arthritic purpuras, 255;  
Abdominal manifestations in rheumatism, 256;  
The incidence of the rheumatic infection, 256;  
A study of the sleeping pulse rate, 256;  
The value of alkali in salicylate administration, 256;  
Malignant hypertension in a girl of 8, 256;  
Two cases of jaundice in infancy, 256;  
A clinical note on convulsions in infants, 257;  
Enuresis of allergic origin, 257;  
Ectopia cordis, 257;  
Boy with bilateral Erb's paralysis feeding himself with his feet, 257;  
Tumours of the parathyroid glands, 257;  
Neoplasm of the suprarenal cortex in an infant of 4½ months, 257;  
Sudden death in infancy and childhood, 257;  
The treatment of hydrocephalus, 258;  
Congenital syphilis, 258;  
Three cases of coeliac disease, 258;  
Some effects of a ketogenic diet, 258;  
Cystic disease of bone in an infant, 258;  
The primary infection of tuberculosis, 258.
- Paralysis, Erb's (K. D. Wilkinson), 257.
- PERRY, C. BRUCE: The electrocardiogram of normal school children, 259—Congenital anomalies of the heart in elementary school children, 265.
- Phosphorus and calcium metabolism in nephritis (Findlay J. Ford), 209.
- Phosphorus compounds and calcium in the blood of children, distribution of (Milan Sokolovitch), 183.
- Pink disease: its morbid anatomy, with a note on treatment (W. G. Wyllie and R. O. Stern), 137.
- Pneumonia in measles (J. B. Ellison), 37.
- Post-anginal sepsis (Mark S. Reuben), 115.
- PRITCHARD, ERIC: Treatment of hydrocephalus, 258.
- Pulse rate, sleeping, study of (Bernard Schlesinger), 256.
- Purpuras, arthritic, role of hæmolytic streptococci in the causation of (F. Langmead), 255.
- Pyloric stenosis, congenital, the chloride metabolism in (Noah Morris and Stanley Graham), 27.
- Pyloric stenosis, congenital hypertrophic (Wilfrid Gaisford), 111.
- Pyuria, non-tuberculous, acute and chronic, in children (A. Victor Neale), 165.
- Race, rheumatism and growing pains (J. C. Hawksley), 303.
- Rammstedt's operation, the surgical anatomy of (Denis Browne), 129.
- REUBEN, MARK S.: Post-anginal sepsis (sepsis of oro-naso-pharyngeal origin), 115.
- Rheumatic infection, incidence of (Leonard Findlay), 256.
- Rheumatism, abdominal manifestations in (K. Tallerman), 256.
- Rheumatism, juvenile (Christopher J. McSweeney), 367.
- Rheumatism, race and growing pains (J. C. Hawksley), 303.
- Salicylate administration, value of alkali in (Stanley Graham), 256, 273—(and Noah Morris), 273.
- SCHLESINGER, BERNARD: A study of the sleeping pulse rate, 256.
- Sepsis, post-anginal [sepsis of oro-naso-pharyngeal origin] (Mark S. Reuben), 115.
- SHELDON, WILFRID (and Eric I. Lloyd): Two cases of double ureter, 231.
- SMELLIE, J. M.: Sudden death in infancy and childhood, 257.
- SOKOLOVITCH, MILAN: Distribution of the phosphorus compounds and calcium in the blood of children, 183.
- SOMERFORD, ANNIE E. (C. P. Lapage and Fanny Howe): Three cases of duodenal obstruction in the newborn, 307.
- SPENCE, J. C.: Nutritional xerophthalmia and night-blindness, 17.
- Spinal tumours in childhood (John Craig and Alexander Mitchell), 11.
- Splenic anaemia, *see* Anæmia.
- Stenosis, pyloric, the chloride metabolism in (Noah Morris and Stanley Graham), 27.
- Stenosis, pyloric, congenital hypertrophic (Wilfrid Gaisford), 111.
- STERN, R. O. (and W. G. Wyllie): Pink disease: its morbid anatomy, with a note on treatment, 137.
- Syphilis, congenital (David Nabarro), 258.
- TALLERMAN, K.: Abdominal manifestations in rheumatism, 256.
- Tattoo tuberculin test, *see* Tuberculin.
- THOMSON, A. P.: Three cases of coeliac disease, 258.
- Tuberculin test, cutaneous multiple puncture (W. S. Craig), 357.
- Tuberculosis, primary infection of (J. Hartley Gibbens), 258.
- Tumours of the parathyroid glands (A. C. Hampson), 257.
- Tumours of the spine in childhood (John Craig and Alexander Mitchell), 11.
- Ulcer, duodenal, perforated, in an infant (L. Priscilla Harrison), 245.
- Undulant fever, *see* Fever.
- Ureter, double, two cases of (Eric I. Lloyd and Wilfrid Sheldon), 231.
- Vomiting of infancy, alkalosis in the (Montague Maizels), 293.
- WARD, KATHLEEN M.: A study of the blood cholesterol in childhood, 329.
- WILKINSON, K. D.: Ectopia cordis, 257—Boy with bilateral Erb's paralysis feeding himself with his feet, 257.
- WINNICOTT, D. W.: Convulsions in infants, 257.
- WYLLIE, W. G. (and R. O. Stern):—Pink disease: its morbid anatomy, with a note on treatment, 137—(and R. W. B. Ellis): The clinical interpretation of some hæmorrhagic states, 313.
- Xerophthalmia, nutritional, and night-blindness (J. C. Spence), 17.

## BETTER MILK FOR BABIES

### FACTS ABOUT LACTOGEN



## Carbohydrates

Compared with maternal milk the carbohydrate content of cows' milk is considerably deficient, but in Lactogen—by suitable modification—this deficiency has been rectified. Unlike ordinary dried milks, in which the carbohydrate is in the same proportion as in the raw milk, LACTOGEN CONTAINS PRACTICALLY THE SAME AMOUNT OF CARBOHYDRATE AS WOULD BE FURNISHED BY HUMAN MILK. Lactogen is neither a new nor untried product. First introduced in Australia, it has for many years enjoyed a large sale in overseas countries.

Lactogen is prepared in England by Nestlé's—famous for more than fifty years for the purity of their milk products—from the pure, fresh milk of specially selected herds grazing on picked English farms.

**Free Samples**  
and detailed description  
thereof will be sent to  
any number of the  
Medical Profession, upon  
request.  
Lactogen Bureau (Dept.  
215) Nestlé and Anglo-  
Siam Condensed Milk  
Co., Ltd. & Proprietors  
LONDON, E.C.3.

**"LACTOGEN"**  
BETTER MILK FOR BABIES

# OSTOMALT

(Ext. Malti c̄ Ostelin Co.)

A comprehensive vitamin preparation, being a combination of "Ostelin" vitamin D, together with vitamin A, the finest malt extract, concentrated orange juice, and calcium glycerophosphate. It contains the vitamin D equivalent of 50 per cent. of cod-liver oil of maximum potency, together with 50 per cent. of orange juice of high anti-scorbutic value. The orange juice, in common with the other components, is physiologically tested for vitamin activity. The addition of a concentrate of vitamin A enables the four vitamins A, B, C and D to be presented in a convenient and extremely palatable form.

HALF-POUND AND ONE-POUND JARS.

GLAXO LABORATORIES, 56, Osnaburgh Street, LONDON, N.W. 1

## A NEW PREPARATION from the Glaxo Laboratories

A high-grade powdered medicinal glucose (98 %) with vitamin D, and an easily assimilable compound of calcium and phosphorus. For use in all cases where glucose is indicated. May be given freely to children and adults.

The low fat diets necessary in acidosis are deficient in vitamin D and generally in calcium. Their presence in this product, besides giving valuable tonic properties, compensates for the deficiency.

# GLUCOSE-D



1-LB. TINS

1/9 PER TIN

Sample tin sent on request to:

GLAXO LABORATORIES, 56, Osnaburgh Street, LONDON, N.W. 1

